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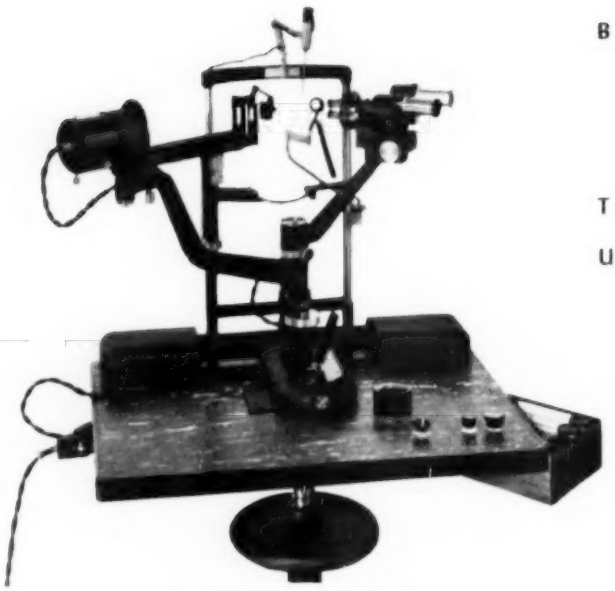

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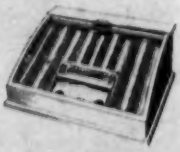

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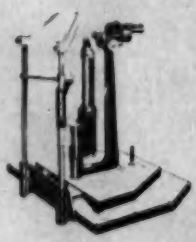

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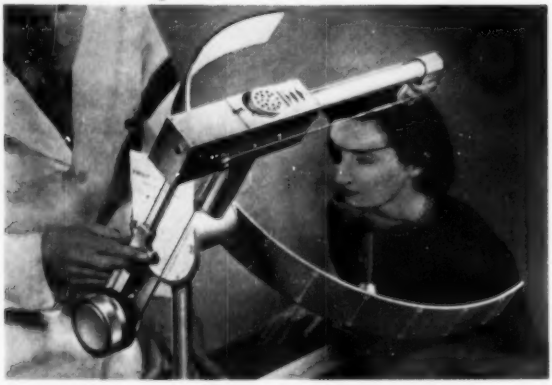

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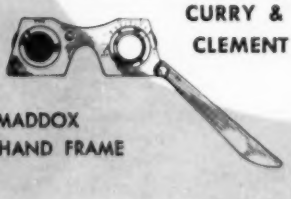

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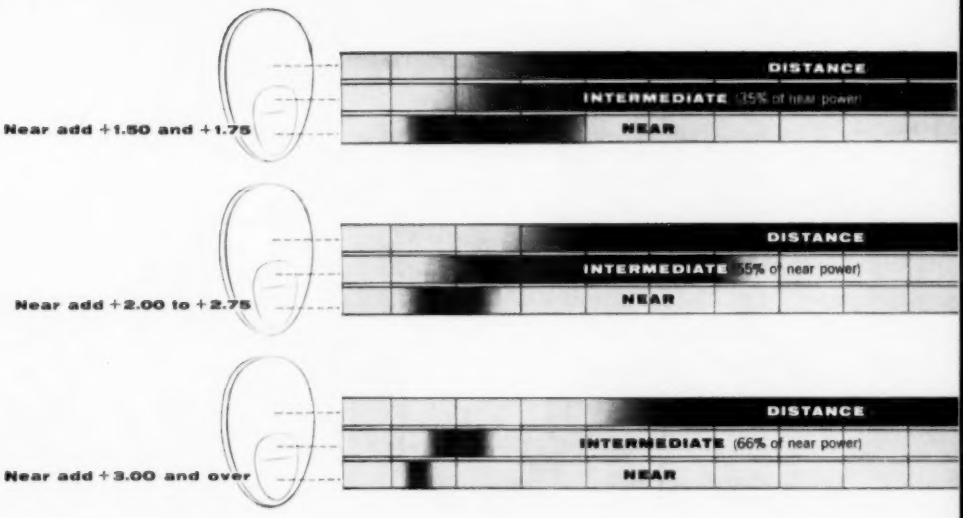

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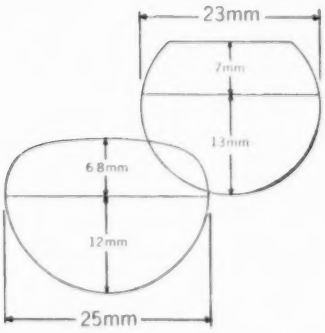

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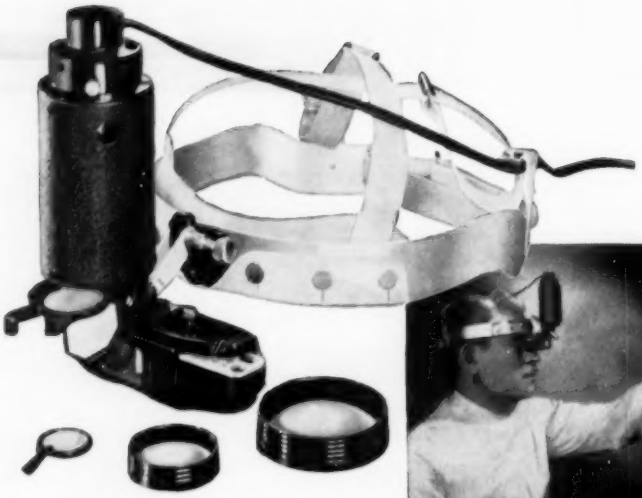

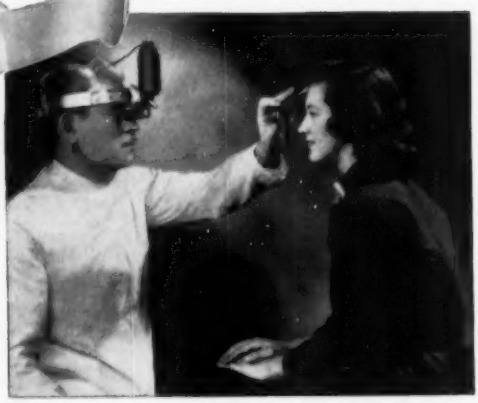

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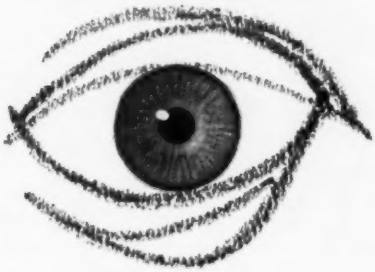

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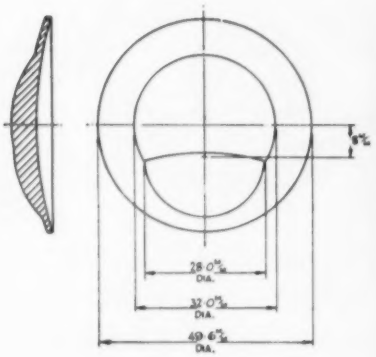

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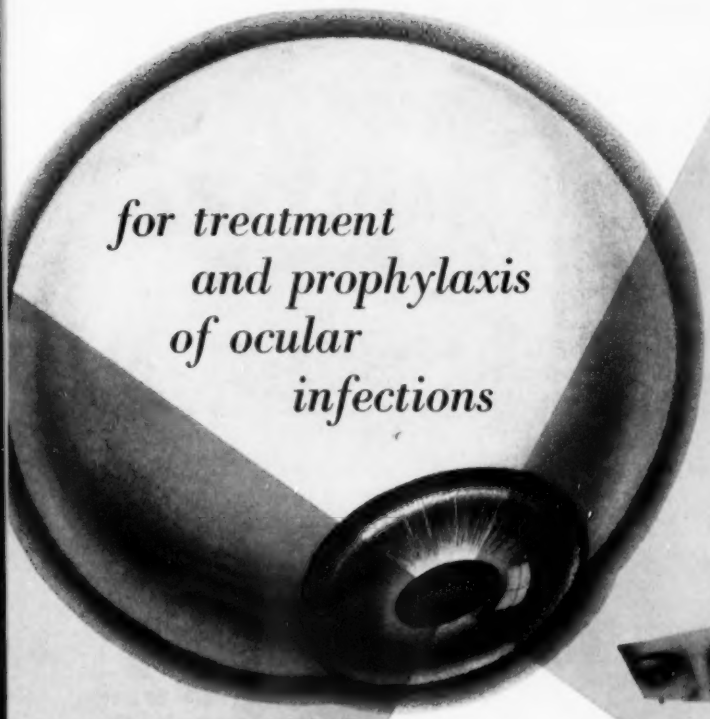

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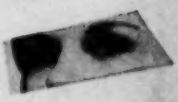

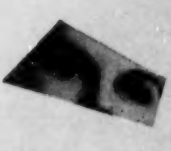

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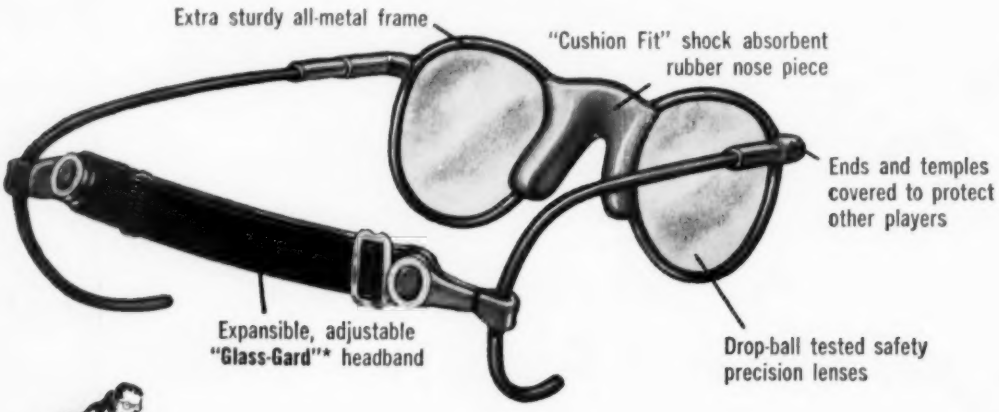
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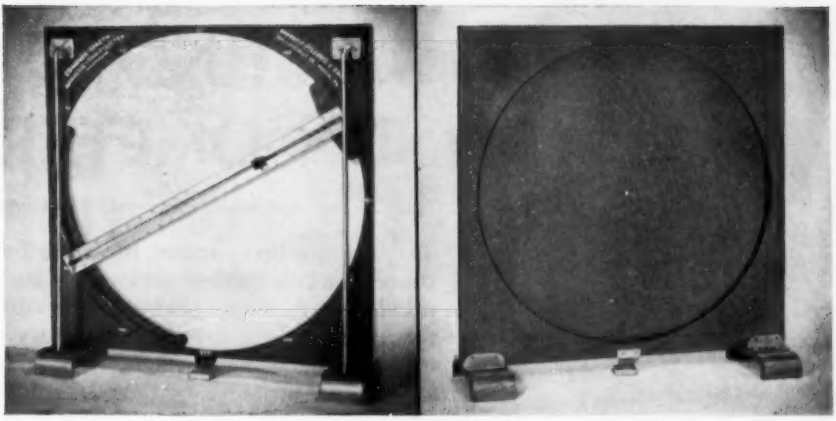

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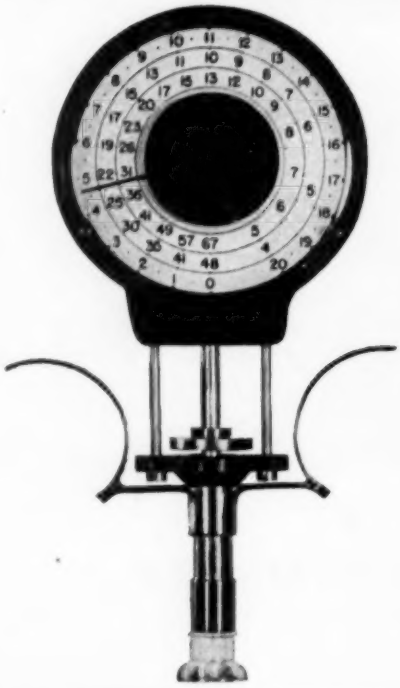

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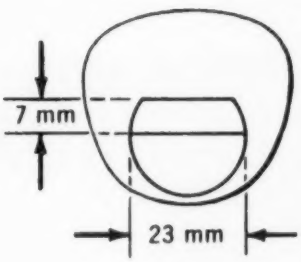

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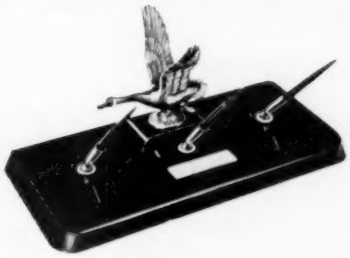

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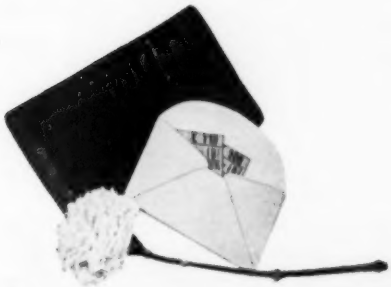

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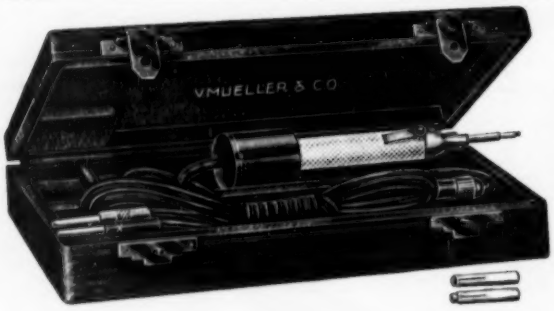

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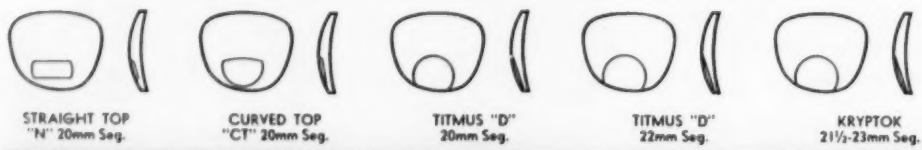

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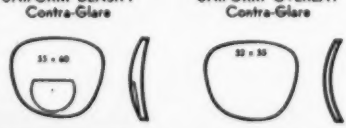

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STRABISMUS SURGERY—MONOCULAR OR BINOCULAR?

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AND
DOROTHY R. BAIR, B.A.
WASHINGTON, D. C.

IT IS THE purpose of this paper to show whether monocular or binocular squint surgery yields a higher percentage of comitance and, if possible, to show whether this factor materially influences the final results of treatment.

The thoughts inspiring this study were these: Since most patients with strabismus do not have a preexisting gross paresis or incomitance, any surgery should attempt to preserve this comitance. Further, monocularity or alternation usually is not influenced by "muscle strength or weakness," but, rather, is affected by ocular dominance, refraction, and amblyopia. Therefore, strabismus should be operated on only with due regard to alignment and preservation of muscle function, not with respect to whether the deviation is alternating or monocular. Finally, it seemed probable that if corresponding muscles in the two eyes were operated on at the same time, comitance could be maintained more easily than if the muscle lengths and insertions of only one eye were changed.

In pursuing the matter further, some questions and answers should be stated. What is the goal in treatment of strabismus, and what factors influence attainment of such a goal? What are the causes of failure, and is incomitance such a cause? Is monocular or binocular surgery more likely to cause comitance—and so to influence success and failure?

The goal in treating strabismus must be the attainment of secure binocular single vision in all possible fields of gaze. When the onset of strabismus is very early, or treatment is instituted late, this goal may not often be attained. Moreover, inaccurate diagnosis and the failure to stabilize binocular alignment by glasses and/or orthoptics after surgery make attainment of this goal difficult. Several years ago, in discussion of the causes of failure in the treatment of squint, a number of causes were cited, such as persistent amblyopia, persistent abnormal retinal correspondence, failure to distinguish the accommodative from the nonaccommodative element, and the difficulty of managing the combined horizontal and vertical deviations; but monocular surgery was not mentioned. More recently, in writing on factors in the cure of squint, the occasion was taken to mention specifically symmetrical treatment as an important factor. This was done without supporting evidence, but from observation of individual cases, often a misleading method of forming conclusions.

In this paper, the effect of binocular symmetrical surgery (i. e., on corresponding muscles in the two eyes) and that of asymmetrical surgery (i. e., on only one eye) will be shown. One seemingly obvious result of asymmetrical surgery would be

"incomitance" (i. e., a different amount of deviation in the several fields of gaze). Evidence of gross incomitance is the obvious limitation of monocular movement, but more discriminating for the smaller degrees of incomitance are (1) the noting of a difference in primary and secondary deviation (i. e., the amounts of deviation when the patient is fixating alternately with the paretic and the nonparetic eye), and (2) the differences in measurement of the deviation in the various positions of gaze (so-called cardinal positions, or cardinal fields).

In order to assure a common understanding, some broad classification of strabismus must be accepted. Such a classification is formulated as follows:

A. Esotropia
   1. Comitant esotropia
      (a) Accommodative—esotropia capable of proper binocular alignment, and whose stimulus to deviation is the accommodation
      (b) Nonaccommodative—esotropia incapable of proper binocular alignment even under favorable conditions
      (c) Combined accommodative and nonaccommodative
   2. Incomitant esotropia, the deviation differing in the several fields of gaze

B. Exotropia
   1. Comitant exotropia
      (a) Intermittent
      (b) Constant
   2. Incomitant exotropia

It is the purpose of the present paper to arrive at certain definite conclusions based on a careful analysis of the surgical results of 535 cases of nonaccommodative and combined esotropia and of 131 cases of exotropia. All patients were examined in private practice by the same two ophthalmologists,* and operated on by one of us (F. D. C.). These facts are important, since the methods of examination and operation were consistent, making the final results comparable. Certain related facts will be commented on also.

I. SCOPE OF SURVEY

Gross incomitance has been found in many postoperative cases in which the results were rather satisfactory as long as gaze was directed in the primary position. Often the esotropic patient who had a recession of one medial rectus alone (or combined with a resection of its directly antagonistic lateral rectus) would have straight eyes in the primary position, exotropia when gazing to the intact side, and esotropia when gazing toward the side of the operation. This would seem to limit the opportunity for binocular single vision to a small range, if it were present at all. It was not known, however, how often this situation would obtain in a large group of patients subjected to monocular squint surgery. Nor was it known how this would compare with a similar analysis of binocular squint surgery.

For purposes of this study, a survey of 3,221 cases of strabismus was made, revealing 2,420 cases of esotropia, 741 of exotropia, and 60 having a vertical deviation only. The cases of esotropia were divided into 596 of purely accommodative type and 1,824 either of purely nonaccommodative type or having a nonaccommodative element. Operation was performed in 901 cases of esotropia, and in 535 of these, there was comitance before surgery and sufficiently exact findings to justify analysis.

* Dr. Marshall M. Parks and one of us (F. D. C.).

Of the 741 cases of exotropia, operation was done in 189, while in 131 findings were sufficiently exact to warrant analysis. It is interesting that in only 50% of the cases of nonaccommodative esotropia was operation performed, and in only 25% of the cases of exotropia was the condition so treated. In part, the reason for this is that many cases of strabismus are of small degree and inconstant in angle; the patient is unwilling to undergo surgery, or visits another ophthalmologist when surgery is suggested. This would seem especially true of the exotropias.

The primary objective was to determine the incidence of definite comitance following surgery. Only those cases were used in which there was a definite statement that ocular rotations or measurements in the lateral fields of gaze (25 degrees to each side of the primary position) were comitant before surgery, and exact postoperative measurements in the lateral fields following surgery were available. Those cases having a difference in alignment of the visual axes of 10 Δ or less in the two lateral fields were considered comitant, while those having a greater difference were considered incomitant.

TABLE 1.—*Scope of Present Survey*

Total cases of strabismus		3,221
Total cases of esotropia		2,420
1. Accommodative	596	
2. Nonaccommodative	1,824	
Total cases of exotropia		741
Total cases of hypertropia		60

While the fixation pattern has been used by many surgeons in deciding whether to operate on one eye or two, in this series the fixation pattern seldom influenced such a choice. Only in deviations of smaller degree or those cases having marked amblyopia was monocular surgery advised. In recent years, even certain patients with extreme amblyopia underwent binocular surgery. In the smaller deviations, also, small amounts of surgery were done to corresponding muscles in each eye frequently, rather than a larger amount to one muscle only.

In the following statistics, it should be noted that the sum of the analyzed subgroups frequently does not equal the total number of cases. Often individual findings were lacking, making exclusion of certain cases necessary.

II. COMITANCE—ITS POSTOPERATIVE INCIDENCE

Upon considering the 665 patients operated on, three groups representing different combinations of surgery were evident. These were (1) patients having corresponding muscles in the two eyes operated on at the same time, (2) patients having monocular surgery and some time later having similar surgery on the other eye, and (3) patients having monocular surgery only.

Among the 538 esotropes, 266 patients had 299 binocular simultaneous symmetrical operations. These consisted of 239 bilateral recessions of the medial rectus, 47 bilateral resections of the lateral rectus, and 13 bilateral marginal myotomies of the medial rectus. Of the 131 patients with exotropia, 102 had 110 binocular

simultaneous symmetrical operations. These consisted of 74 bilateral recessions of the lateral rectus, 4 bilateral tenotomies of the lateral rectus, and 32 bilateral resections of the medial rectus.

Of the patients who had binocular simultaneous symmetrical surgery (bilateral recession, bilateral resection, or bilateral marginal myotomy), 235 esotropes had one session of surgery, while 31 had two such operations. Of these 266 patients, only 94 had adequate immediate postoperative measurements. Eight-two (87%)

TABLE 2.—*Scope of Present Survey: Analysis of Operations*

No. of operations analyzed		665
Esotropia		535
Bilateral simultaneous	266	
Unilateral + "symmetrizing"	38	
Unilateral only	231	
Exotropia		131
Bilateral simultaneous	102	
Unilateral	28	

TABLE 3.—*Incidence of Postoperative Comitance: A. Binocular Simultaneous Symmetrical Surgery*

	Comitance	Incomitance
1. Esotropia (266 cases)		
(a) Within 6 wk. postoperatively	82 (87%)	12 (13%)
(b) At final examination	255 (96%)	11 (4%)
2. Exotropia (102 cases)		
(a) Within 6 wk. postoperatively	50 (98%)	1 (2%)
(b) At final examination	100 (98%)	2 (2%)

Conclusion: Symmetrical surgery results in a high percentage of comitance.

TABLE 4.—*Incidence of Postoperative Comitance: B. Monocular Surgery, with Similar Surgery on Other Eye Later**

	Comitance	Incomitance
1. After monocular surgery	20 (53%)	18 (47%)
2. After "symmetrizing" surgery	31 (82%)	7 (18%)

Conclusion: The incomitance of monocular surgery may often be made comitant by similar surgery on the eye not previously operated on.

* Number of cases, 38.

of these were immediately comitant, while 12 (13%) were incomitant. However, at the final measurement (averaging 18 months after surgery), 255 (96%) were comitant and only 11 (4%) were incomitant.

Similar analysis of 102 exotropes showed an even more striking outcome. Of 51 patients having adequate immediate postoperative measurements, 50 (98%) were comitant, and only 1 (2%) was incomitant. This same percentage was maintained at the time of the final measurement (averaging 18 months after operation), showing 100 cases of comitance and only 2 of incomitance.

From these figures it would be reasonable to conclude that binocular symmetrical surgery results in an extremely high percentage of comitance (which is most

striking in the exotrope) and that the passage of time does not greatly influence this relationship. In such surgery on the esotrope a slightly lower percentage of comitance results immediately, but at the final measurement this had further improved, almost equaling that for the exotropes. Comitance is the rule in binocular simultaneous symmetrical surgery.

Another group of interest consists of those patients who had monocular surgery (i. e., recession or resection or both on the same eye) initially and at some later time had similar ("symmetrizing") surgery performed on the other eye. Of 38 such patients, 20 (53%) were comitant and 18 (47%) were incomitant after surgery on the first eye. However, after similar surgery on the second eye, 31 (82%) were comitant, and only 7 (18%) were incomitant. It is, then, very

TABLE 5.—*Incidence of Postoperative Comitance: C. Monocular Surgery Only**

	Comitance	Incomitance
(*a*) Within 6 wk. postoperatively	34 (35%)	63 (65%)
(*b*) At final examination	124 (48%)	135 (52%)

Conclusion: In monocular surgery incomitance is the rule, though comitance increases somewhat with the passage of time.

* Number of cases, 259.

TABLE 6.—*Incidence of Postoperative Comitance: C. Monocular Surgery*

	Comitance	Incomitance
1. Recession only	83 (58%)	59 (42%)
2. Recession + resection	41 (39%)	65 (61%)
3. Resection only	0	9 (100%)

TABLE 7.—*Incidence of Postoperative Comitance: D. Summary*

	Comitance	Incomitance
1. Binocular simultaneous surgery	355 (96%)	13 (4%)
2. Monocular + symmetrizing	31 (82%)	7 (18%)
3. Monocular only	124 (48%)	135 (52%)

apparent that in this group incomitance often results from monocular surgery, and that in a considerable percentage of cases comitance follows similar surgery on the second eye.

The final group for investigation comprised the 259 heterotropes having monocular surgery only. Of 231 esotropes so operated on, only 87 had adequate immediate postoperative measurements, and of these, only 34 (35%) were comitant, while 63 (65%) were incomitant. It is interesting to note, however, that at the time of final measurement (averaging 30 months after surgery), 124 (48%) were then comitant and 135 (52%) were still incomitant.

The thought occurred that possibly all combinations of monocular surgery did not present such a high percentage of incomitance. Further analysis showed that when unilateral recessions only were considered, 83 (58%) of patients maintained comitance, while 59 (42%) became incomitant. The recession and resection on one eye resulted in 41 (39%) comitant and 65 (61%) incomitant. While only

nine unilateral resections alone were done, they all resulted in incomitance. Thus, the operation of choice would seem to be the unilateral recession, if monocular surgery must be done.

The final comitance obtained in monocular surgery (48%) does not compare favorable, as would be expected. Of 260 patients with comitance, 178 (68%) the 82% obtained when one eye is operated on at one session and similar surgery is done on the other eye at another time. We are forced to conclude that if comitance is desirable, binocular simultaneous symmetrical surgery should be done.

III. INFLUENCE OF FIXATION PATTERN ON POSTOPERATIVE COMITANCE

Much emphasis has been placed upon the type of fixation (monocular or alternating—heteronymous, homonymous, or indiscriminate) present in any given case of strabismus. Some surgeons would plan surgery largely upon the type of preoperative fixation present. However, monocularity and alternation are not of necessity influenced by muscle strength or weakness or by limited or excessive ocular movements. Probably the homonymous or heteronymous pattern in alternating strabismus is not so influenced, either. It is not uncommon to find the paretic eye fixating by choice in cases of gross paralytic strabismus. Similarly, it is not unusual in less obvious cases of paretic strabismus to find the paretic eye fixating under all circumstances, even when the direction of gaze makes such fixation most inconvenient.

TABLE 8.—*"Fixation" and Postoperative Comitance*

	Comitance	Incomitance
1. Monocular fixators (424 cases)		
(a) Binocular surgery	215 (97%)	6 (3%)
(b) "Symmetrizing" surgery	17 (85%)	3 (15%)
(c) Monocular surgery	194 (56%)	79 (44%)
2. Alternating fixators (241 cases)		
(a) Binocular surgery	143 (97%)	4 (3%)
(b) "Symmetrizing" surgery	16 (88%)	2 (12%)
(c) Monocular surgery	36 (47%)	40 (53%)

The type of fixation is probably determined by the innate ocular dominance, the degree and type of anisometropia, if any, and the resulting or coincidental amblyopia present, rather than by muscle strength or weakness.

In this study, type of fixation rarely influenced the selection of surgery to be performed. Rather, all patients were urged to have binocular surgery. Only in cases of deep amblyopia or disease severely affecting vision in one eye (not in all of these) and in cases of small angle squints was monocular surgery done.

There are no commonly accepted criteria for distinguishing the true alternating, the "almost" alternating, and the true monocular fixators. We have arbitrarily included among the "alternators" all patients who spontaneously alternate or whose eyes have equal refractive errors and equal vision. This includes most congenital esotropes, most intermittent exotropes, and all "true" alternators.

Of 665 patients, 241 (36%) were classed as "alternating," while 424 (64%) were termed "monocular" fixators. Since no distinction was made in planning the type of surgery for these two groups of cases, it is interesting to note the postoperative comitance or incomitance present after various combinations of surgery.

Monocular surgery was performed on 183 monocular fixators and resulted in 104 (56%) being comitant and 79 (44%) incomitant. When monocular surgery was done on 75 alternating fixators, 36 (47%) were comitant, while 40 (53%) were incomitant. From this, it would appear that monocular surgery on monocular fixators results in a somewhat higher percentage of comitance than when such surgery is performed on alternators.

When binocular surgery was performed on 221 monocular fixators, 215 (97%) had postoperative comitance, while only 6 (3%) were incomitant. It is interesting that when similar binocular surgery was performed on 147 alternators, 143 (97%) were comitant and 4 (3%) were incomitant. We might conclude from these figures that binocular surgery gives high and equal percentages of comitance in monocular and alternating fixation. If monocular surgery is to be performed, it probably should be reserved for monocular rather than the alternating fixators.

IV. POSTOPERATIVE COMITANCE—ITS SIGNIFICANCE

It having been shown that monocular surgery often leads to incomitance, much of which persists, and that bilateral symmetrical surgery usually leads to comitance, it becomes important to decide what influence comitance or incomitance has upon the eventual cures.

As has been mentioned before, it would seem that incomitance would so reduce the opportunity for binocular vision that secure binocular vision (and cure of squint) could not develop. However, this is not necessarily true. We may recall cases of gross congenital incomitance in which very good binocular single vision exists in the fields in which binocular alignment is possible, while suppression takes place in the fields in which the deviation exists. For example, of some 20 cases of congenital "paralysis of the inferior oblique," 16 have binocular single vision in the lower fields and in the fields opposite that of the involved muscle, while transitory diplopia and suppression occur in the field of action of the involved muscle. A similar situation exists when some 40 cases of Duane's retraction syndrome are considered. Binocular single vision was present in 30 cases and probably present in 9 more, with some turning of the head toward the uninvolved side, but suppression existed when gazing in the field of action of the fibrotic (?) lateral rectus.

These examples might cast some doubt upon the importance of comitance in the developing and maintaining of binocular single vision. The same doubt might reasonably be cast upon the significance of postoperative comitance in the development of binocular single vision.

In the simplest terms, the goal in treating strabismus is to obtain straight eyes, comitance, and normal retinal correspondence. It is reasonable to assume that any patient having straight eyes, comitance, and normal retinal correspondence may eventually develop adequate fusion and a cure result. It is important, then, to see whether the factors of straight eyes and normal retinal correspondence are materially influenced by the presence or absence of comitance. It was recognized early in the study that congenital heterotropia, in which there is no early opportunity for binocular single vision, must be distinguished from the heterotropia of later onset, in which there has been such an opportunity. The present analysis was made in these two groups of cases of heterotropia, showing the relations of the three factors named above.

Of 198 patients with congenital strabismus in whom surgery had produced comitance, 106 (54%) had straight eyes and normal retinal correspondence, while of 61 patients with incomitance, only 19 (31%) had such a favorable outsome. Among the remaining patients with congenital squint, equal percentages of the incomitant and the comitant had straight eyes but abnormal retinal correspondence (15%), and almost equal percentages had a residual deviation and normal retinal correspondence (15 to 16%). However, in the group least favorable to final cure (i. e., residual deviation and abnormal retinal correspondence) a much higher percentage was incomitant (36%) than comitant (15%). We may conclude that of patients with congenital heterotropia, favorable findings (straight eyes and normal retinal correspondence) are most frequent in those having comitance after surgery. On the other hand, the group with incomitance presents the highest percentage of unfavorable findings (residual deviation and abnormal retinal correspondence).

In patients with strabismus of later onset, the findings are similar but more favorable, as would be expected. Of 260 patients with comitance, 178 (68%) also had the favorable findings of straight eyes and normal retinal correspondence.

TABLE 9.—*Significance of Postoperative Comitance*

		Straight and N. R. C.*	Straight and A. R. C.*	Residual and N. R. C.	Residual and A. R. C.
A. Congenital					
1. Comitant	(198)	106 (54%)	31 (15%)	31 (15%)	30 (15%)
2. Incomitant	(61)	19 (31%)	10 (15%)	10 (16%)	22 (36%)
B. Later onset					
1. Comitant	(260)	178 (68%)	11 (4%)	36 (14%)	35 (14%)
2. Incomitant	(81)	30 (37%)	4 (5%)	25 (32%)	21 (26%)

* Normal retinal correspondence; abnormal retinal correspondence.

On the other hand, of 81 having incomitance, only 30 (37%) had straight eyes and normal retinal correspondence.

While no definite cause-and-effect relationship can be established between comitance, on the one hand, and straight eyes and normal retinal correspondence, on the other, the association in this series seems significant. The patient with comitance has a definitely greater chance of eventual cure.

V. MISCELLANEOUS COMMENT

Several additional thoughts of interest have arisen in this investigation.

We noted that after monocular surgery, comitance increased from 35%, immediately following surgery, to 48%, at the time of final measurement (averaging 30 months after surgery). We wondered how rapidly the 13% who converted from incomitance to comitance did so. A pilot study of these cases suggests that 50% had converted to comitance in the first six months, 64% within the first year, 79% in two years, 90% in three years, and all in four years. This does not mean that all patients with incomitance after surgery eventually become comitant; rather, it means that of those who did become comitant, the transition was completed in all within four years.

While statistical evidence is not available, it is our impression that a definitely larger group of patients have asymmetry of the palpebral fissures and asymmetrical

proptosis or enophthalmos following monocular surgery than following binocular surgery. It is reasonable to expect that the monocular relaxing or tightening of extraocular muscles might widen or narrow the palpebral fissure and retract or advance the globe. Exact measurements and data were not available in this series.

Another point of interest was the influence of binocular surgery on the near point of convergence in esotropia. Again, while statistical data are not easily available, it is our impression that the near point of convergence is unfavorably influenced no oftener by a conservative recession of both medial rectus muscles than by a recession and resection on one eye only. Also, while a bilateral resection of the lateral rectus seldom produces a remote near point of convergence, it seldom improves the strabismus greatly. In general, it was a disappointing procedure in our hands.

It should be understood that in strabismus in which an obvious incomitance exists before surgery, we have frequently done monocular surgery, or asymmetrical surgery involving noncorresponding muscles in each eye. Incomitant strabismus requires surgery on the underacting and/or overacting muscles, and operation on corresponding muscles in each eye will usually not be indicated.

VI. SUMMARY AND CONCLUSIONS

A series of 665 cases of strabismus, with all operations performed by the same surgeon, is analyzed. Special emphasis is placed upon the incidence of postoperative incomitance and the influence such incomitance has upon the final results of treatment. The following conclusions may be drawn:

1. Postoperative comitance is more frequently present when binocular simultaneous symmetrical surgery has been performed.

2. In such symmetrical surgery, the comitance is not influenced by the pattern of preoperative fixation.

3. Incomitance occurs in a high percentage of cases in which monocular surgery only has been performed and persists in over 50% of the cases.

4. If monocular surgery is followed by similar surgery on the other eye at another time, the existing incomitance can often be converted to comitance.

5. When postoperative comitance exists, the favorable findings of straight eyes and normal retinal correspondence are more frequently present than when incomitance results from surgery. The presence of comitance, normal retinal coresponding, and straight eyes is favorable to a final cure.

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SURGICAL MANAGEMENT OF NONPARALYTIC EXOTROPIA

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IN REVIEWING the literature on the surgical treatment of strabismus, one is impressed by the fact that most of the recent reports have dealt with the management of the vertical muscles and esotropia. The paucity of reports on exotropia may mean that to many ophthalmologists this type of case presents no problem. We have been impressed, however, by the many types of operative procedures utilized by various surgeons in attempting to correct exotropia. Recently, while reviewing the surgical results in a series of intermittent exotropias, one of us (R. D. M.) was surprised to find that in a group of 31 clinic patients, 40 operations had been performed utilizing 13 different types of surgical procedures. We realize that the various combinations of operative procedures which are theoretically possible with the lengthening and shortening of the four lateral rectus muscles is greater than 13, but we do not believe that basically there is any need for so many procedures to correct the same condition. This is the main reason for our interest in this subject.

Orthophoria is defined as that state of muscle imbalance which exists when the eyes remain parallel for distance and assume the proper convergence for near even if fusion is suspended. Heterophorias are relative deviations of the visual lines which are kept latent by the fusion impulse. When the fusion impulse is absent or suspended, the latent heterophoria may become a manifest deviation, or heterotropia. If the visual line of an eye diverges relative to that of the other eye, exotropia is said to exist. It may be intermittent, alternating, or constant. In this paper we are considering only the nonparalytic exotropias.

We shall not discuss the great and mysterious factor called fusion, as it is outside the scope of this paper. However, it is especially within the realm of the intermittent tropias that the presence or absence of fusion is a determining factor.

There are some people who have the ability to fuse, but who have a high heterophoria. When these people become tired or inattentive, when they are ill, or when they are in the throes of an emotional upheaval, they are not always able to keep their eyes straight. Their eyes change from a heterophoria to a heterotropia. These patients are classified as cases of intermittent strabismus. The term periodic, which is also used for these cases, implies, according to Chavasse, a regularity in the cycle of latency and should therefore not be used.

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The patient with an alternating exotropia can fix with either eye, and he may change fixation spontaneously. It is obvious from the character of an alternating squint that the vision in the two eyes is usually the same, and he fixes with whichever eye is more convenient to use.

The patient with a constant exotropia always fixes with the same eye, while the other eye is divergent. In this type of case the divergent eye is frequently amblyopic.

The term postoperative exotropia, at least as used by us, implies that before any operative procedure was done the patient did not have an exotropia. Most postoperative exotropias are the result of an overcorrected esotropia.

Much has been written concerning the etiology of heterotropia. There are generally two factors to be considered, the anatomical and the physiological components. The anatomical factors include the size and shape of the globes and orbits, the insertions of the muscles, and their fascial connections. The physiological, or innervational, factors, which have been well covered by Adler,[1] encompass the fixation and fusion impulses, vestibular influences, nuclear and supranuclear areas, and the relationship of convergence, divergence, and accommodation which exists. While other factors may play a part in the etiology, it is obvious that in the surgical treatment one can influence only the anatomical factors, since one cannot operate on a divergence center even if it does exist.

We have used a simple classification of nonparalytic exotropias, but it appears adequate from the viewpoint of surgical management:

1. Intermittent exotropia
2. Alternating exotropia
3. Constant exotropia
4. Postoperative exotropia

Cases of exotropia should be handled in the same way as any other type of heterotropia. This includes history taking, refraction, and muscle balance and orthoptic evaluation. There is no question that orthoptic exercises are of great value in this type of case, but we believe that if a definite exotropia is present, operation should be performed even before the age when the child can cooperate intelligently.

The two main indications for surgery in exotropia are, first, binocular function with fusion, our ultimate goal, and, second, cosmetically straight eyes. The latter, we believe, can usually be obtained if the proper surgical procedure is employed, and the former can be accomplished if surgery is done early and physiological function restored soon enough for fusion to develop and be maintained.

Chavasse [2] has stated that normal retinal correspondence is particularly common in divergent strabismus, especially if it is of the intermittent type. The acquisition of anomalous retinal correspondence in strabismus is one way of avoiding diplopia. Another method is suppression. In our series no attempt was made to correlate the sensory correspondence with the surgical results. These data were not available for some of the clinic patients, and many of our private patients were too young for full sensory evaluation. It is our opinion that, while normal sensory correspondence is desirable, it probably does not seriously influence the surgical result.

Duthie [3] estimates that in 8 to 10% of all cases of strabismus the eyes are divergent. He states that phorias present problems of symptoms, and convergent squints, those of appearance and defects of binocular vision, while cases of divergent

squint frequently embrace all three complaints. The incidence of divergent strabismus at the Wills Eye Hospital clinic is approximately 18% of all cases of strabismus and 0.2% of the total admissions.

Burian [4] believes it to be a fallacy to base the choice of operation on the behavior of convergence and divergence, and in this we are in complete agreement. We prefer to base the type of surgery on the ocular rotations.

Peter [5] has stated that surgical procedures are less satisfactory in divergent than in convergent squints. We cannot agree to this, especially as it applies to cases of intermittent exotropia.

Lee and O'Brien [6] have given a definite plan of the surgical procedures to be followed, depending upon the degree of deviation present. They also state that the results are extremely variable, even with a standard technique in the hands of the same surgeon.

The surgical techniques that we advise are not original. We are surprised, however, to see that some surgeons use extreme care in intraocular surgery and yet their muscle surgery appears rather haphazard. In brief, we believe that the initial conjunctival incision should be about 6 to 7 mm. from the limbus and well below or above the insertion of the muscle. The incision should be carried down to sclera and then the muscle secured on a muscle hook. The incision should then be enlarged upward or downward and should include conjunctiva only, avoiding the vessels overlying the insertion of the muscle. Once the muscle insertion is exposed, the suture of the surgeon's preference is placed through the insertion and the muscle freed from the globe. The conjunctiva is then freed toward the canthus, precaution being taken to preserve the muscle sheath intact. In recession operations, especially, all intramuscular membranes should be cut and the muscle freed so that a muscle hook can be pushed freely into the orbit. In the case of the external rectus the inferior oblique should be isolated and precautions taken not to cut it. The avoidance of undue hemorrhage, the preservation of the muscle within its sheath, and the cutting of the intermuscular membranes, especially if they are thick membranous extensions, give the minimal postoperative reaction and the most satisfactory functional result.

At the risk of appearing dogmatic, we feel the following procedures are usually necessary in the cases of exotropia as we have classified them. We believe that all intermittent exotropias sufficient to cause symptoms or to be cosmetically noticeable should be treated surgically, regardless of the age of the patient. The choice of operation is usually a bilateral recession of the external rectus to the equator, regardless of the degree of squint present. If the near point of convergence is remote, a bilateral internal rectus resection may be advisable. Whatever surgical procedure is decided on, we feel it should be bilateral and symmetrical. A slight overcorrection in the immediate postoperative period is desirable.

Alternating exotropia should have bilateral symmetrical surgery unless there is definite preference for one eye. In smaller degrees of squint a bilateral recession of the external rectus muscles may suffice. A bilateral resection of the internal rectus is usually indicated in the larger degrees of squint, and in some cases both procedures may be required. We do not favor operation on four muscles at one time. If there is a marked ocular dominance, the surgery may be confined to

the two horizontal muscles of the nondominant eye. As in the case of intermittent exotropia, a slight overcorrection in the immediate postoperative period is more likely to result in a functional cure.

In constant exotropia one is usually aiming at a cosmetic result only, as the divergent eye is usually amblyopic. In these cases we believe that the primary surgery should be confined to the amblyopic, or divergent, eye. Our choice is a resection of the internal rectus with recession of the external rectus muscles. The maximum amount of surgery is usually done, since it is difficult to overcorrect this type of exotropia.

The treatment of postoperative exotropias is usually more difficult. More surgery is required to correct an overcorrected esotropia than was necessary to produce the overcorrection in the first place. If the original operation was a recession of the internal rectus muscle and a divergence resulted, a mere replacement of the internal rectus to its original insertion will not be sufficient. One must usually advance or resect the internal rectus and recess the external rectus before parallelism can be achieved. If possible, one should be familiar with the original deviation and what procedure resulted in the overcorrection before a logical plan can be formulated to correct the postoperative exotropia. Generally speaking, the same muscles or muscle that was originally operated on should be the first to be reoperated on. As a rule, it takes twice the amount of surgery to correct an overcorrection as it did to produce the overcorrection in the first place.

Our postoperative care is fairly simple. Patients who have had a bilateral recession of the external rectus muscle have their patches removed in 24 hours and are encouraged to read and do close work. When a muscle has been resected, both eyes are usually patched for 48 hours; after this the eye or eyes operated on are patched only if there is undue reaction. Orthoptic exercises are resumed as soon as feasible and are continued if it is apparent that a functional cure is possible.

We have reviewed the records of 147 patients operated on at the Wills Eye and Lankenau Hospitals during the past three years. There were 15 types of operative procedures done on these patients, performed by a number of surgeons. The average age of the patients at the time of operation was 15.2 years, and the average hospital stay, eight days. The results are classified as excellent when the eyes are straight and fusion is present and as good when the eyes cosmetically were straight, with less than 5 degrees of esotropia or exotropia on cover, but no fusion was present. "Improved" signifies cosmetic improvement with less than 10 degrees of exotropia remaining, and "poor" indicates that the exotropia remained greater than 10 degrees.

The results of these cases are tabulated as follows:

		Excellent	Good	Improved	Poor
Intermittent exotropia		8	7	8	2
Alternating exotropia		6	15	10	10
Constant exotropia		1	25	20	17
Postoperative exotropia		1	6	5	6
Total patients	147	16	53	43	35
		11%	36%	29%	24%

It is apparent that while 76% of the patients were improved by their surgery, only 47% had straight eyes.

From this larger series we separated and analyzed the records of 38 private patients operated on by us during the past two years. The techniques advocated by us were followed. In this smaller series we found 18.4% with excellent results, 60% with good results, 18.4% with improvement, and 3.2% with poor results. Thus, the exotropia of 97% was improved with surgery, and 78% had straight eyes. It is apparent that simple surgical techniques, performed in what we consider a logical manner, produced quite satisfactory results.

SUMMARY

The terminology and some of the etiological factors in nonparalytic exotropia are briefly defined. We have reviewed 147 cases of exotropia and have classified them as intermittent, alternating, constant, and postoperative. In the first two types bilateral symmetrical surgery is usually indicated. A bilateral recession of the external rectus muscles is indicated unless the near point of convergence is remote; if so, a bilateral resection of the internal rectus muscles is the operation of choice. In constant exotropia the surgery is usually confined to the amblyopic eye and consists of a maximal recession and resection. In postoperative exotropia a greater amount of surgery is required to correct the overcorrection than was done to produce the undesired result.

The surgery should be relatively atraumatic, and if a muscle is to be recessed, any dense intermuscular membranes should be severed. Preservation of the muscle sheath and avoidance of hemorrhage result in fewer adhesions and better function of the muscle.

Adherence to these simple principles will usually effect a satisfactory result.

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ANOMALOUS RETINAL CORRESPONDENCE IN ALTERNATING STRABISMUS

Incidence and Influence on Postoperative Results

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IT SEEMS that many practicing ophthalmologists, especially residents in ophthalmology, have an erroneous idea that anomalous retinal correspondence cannot exist in a case of alternating squint or in cases in which there is equal vision in the two eyes.

The belief that anomalous retinal correspondence is rare in alternating strabismus probably arises from the conflicting views expressed by various authors. Thus, Kramer * states: "It is interesting but as yet unexplainable why anomalous retinal correspondence is predominately associated with amblyopia exanopsia." Strazzi,[2] in studying 80 patients, 60 of whom had uniocular strabismus, also states: "A prevalence of anomalous retinal correspondence was noted in patients with amblyopia." Stephenson [3] stated that anomalous retinal correspondence is more prominent in unilateral squint than in essential alternating squint. But he adds that it does develop in an appreciable number of cases of alternating squint.

On the other hand, Lyle † states:

> There is a class of alternating convergent squints in which the onset is early, the squint is symmetrical, the visual acuity is practically equal, the refraction is normal, and in these cases which are sometimes described as essential alternating squints, positive secondary sensory correspondence is practically universal and developed to the highest degree.

Muegge,[5] in 1911, reported that 61.5% of patients with alternating and 27.4% of patients with uniocular squint had anomalous retinal correspondence. Pugh,[6] in 1934, reported that 77% of patients with alternating and 23% with uniocular squint had anomalous retinal correspondence; finally, Adler and Jackson,[7] in 1947, reported that 83% of patients with alternating and 52% with uniocular squint had anomalous retinal correspondence. The last three papers all indicate a high incidence of anomalous retinal correspondence in so-called alternating strabismus. Travers [8] even goes so far as to say that anomalous retinal correspondence prevents the development of amblyopia.

These conflicting views may also be due to the fact that different testing methods were used and, hence, different results were obtained. It is well known that a patient can show normal retinal correspondence on the after-image test and anomalous

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* Kramer,[1] p. 345.

† Lyle,[4] p. 200.

retinal correspondence on the synoptophore. Another explanation for the variety of opinions may be in an author's definition of anomalous retinal correspondence. Many authors do not consider retinal correspondence abnormal unless the patient can actually superimpose dissimilar targets at a subjective angle different from the objective angle. This they call true abnormal retinal correspondence, or positive secondary sensory correspondence. If, however, there is suppression at the subjective angle, they refer to it as lack of normal retinal correspondence, or negative secondary sensory correspondence. Both these latter terms are vague and confusing, and it would be better to call the condition atypical abnormal retinal correspondence, as does Kramer.‡ Actually, atypical abnormal retinal correspondence is commoner than is typical abnormal correspondence. Hence, one who uses the former terminology would have a high incidence in his series of cases, while one using the latter terminology of true, typical, or positive abnormal correspondence would have a low incidence in his series of cases. From a practical standpoint, retinal correspondence must be either normal or abnormal; therefore, I prefer to call any correspondence abnormal in which the two foveas no longer have common visual directions, regardless of the type of suppression pattern that the patient may have. In this paper both typical and atypical anomalous correspondence will be referred to as anomalous correspondence.

Another reason for the belief that patients with alternating strabismus cannot have anomalous retinal correspondence is the misconception that total alternate suppression occurs in these cases. Total alternate suppression is rare as compared with regional suppression, which is common. This has been proved by Travers,[8] who showed suppression scotoma over the macula in cases of squint with normal retinal correspondence and suppression scotoma over an extramacular region when anomalous correspondence was present. He further showed that the scotoma may vary in size, and may even alter its position, with direction of gaze. The size of the scotoma varies inversely with the visual acuity of the suppressed area. Therefore, it is very small when the suppressed area is over a macula with normal vision, larger when over a macula with amblyopia, and larger still when over an extramacular area, as occurs in cases of anomalous correspondence with a large angle of anomaly. This observation shows that suppression is not related to retinal correspondence and that it is almost always regional, and rarely total. If one understands these characteristics of retinal suppression, one must agree with Julia Lancaster,[9] who states:

> There is nothing in my experience to show that alternating strabismus cases behave any differently from any other type of strabismus patients in developing fusion.

My interest in alternating strabismus was aroused when it became apparent that a certain number of the cases were postoperative failures. The surgery had been satisfactory and thus some other reason for failure was suspected. The sensory correspondence was carefully studied, and it was found that in most of these patients there was a deeply rooted anomalous retinal correspondence. It was also noted that these particular patients had a troublesome postoperative paradoxical diplopia.

With this point in mind, records were reviewed, and patients with alternating strabismus were recalled in order to check their sensory correspondence when this had not been done previously. The term alternating strabismus is used rather

‡ Kramer,[1] p. 353.

loosely in order to include patients with equal vision, as well as those whose visual acuity was within two lines' difference on the Snellen chart. It was felt that these patients should have the best opportunity for developing normal binocular vision postoperatively.

The cases were tabulated as to the age of onset, visual acuity, effect of lenses, age when treatment was started, type of sensory correspondence, and postoperative result. I saw all patients personally and examined them for anomalous retinal correspondence. The synoptophore and after-image tests were performed on all patients. In general, if the child was under 5 years of age, the after-image test was unsatisfactory, whereas the synoptophore test was more satisfactory even with a child as young as 2½ years of age. The diplopia and Lancaster red-green tests were also used at times when it was desirable to make certain of equivocal findings, since it is well known that the state of sensory correspondence may vary from day to day or with different testing methods. The after-image test was performed in a darkroom in order to determine positive after-images. It was felt that if the patient could recognize the proper sequence of color changes, as is seen with positive after-images, one had an additional check on the reliability of the patient's answers. Since all patients had 6/12 or better vision, a displacement of after-images due to fixation anomalies in amblyopia would not be more than 0.8 degree as shown by Brock and Givner.§ Hence, the interpretation of this test for anomalous correspondence should be correct. No orthoptic treatment was given to any of these patients, except for postoperative alternate occlusion in four cases and preoperative orthoptic training for one month in Case 5 (Table 1) to correct an anomalous correspondence. (The orthoptic treatment was unsuccessful until one week after operation, when the retinal correspondence became normal.)

Table 1 is a summary of the 76 cases used in this study. The first 51 cases in this series came from 102 unselected active squint records in our clinic. It is rather interesting to note that of 102 unselected cases, 50% showed either equal vision or vision within two lines' difference on the Snellen chart. The remaining 25 cases making up this series were selected specifically because of the equal, or nearly equal, vision in the two eyes. Of these 76 cases, operation was done in 53, and, of these, 42 were followed for one year or more after operation and 11 followed for less than one year.

Table 2 shows the incidence of anomalous correspondence in relation to age of onset and type of squint. It can be seen from this Table that in cases of esotropia developing before 3 years of age abnormal retinal correspondence was found in 64%, normal retinal correspondence in 24%, and equivocal correspondence in the remaining 12%. In cases of esotropia developing after 3 years of age, retinal correspondence was abnormal in 20%, normal in 69%, and equivocal in 11%.

The cases of exotropia appear to be too few in number to be of statistical significance, but it can be seen that anomalous correspondence was found more frequently than one might expect.

Table 3 is an analysis of the 41 cases showing anomalous correspondence. Of these 41 patients, 22 showed anomalous correspondence with the after-image test, as well as on the synoptophore; 10 were tested on the synoptophore alone; 4 showed anomalous correspondence on the synoptophore but normal correspondence in the after-image test, and 5 showed both normal and abnormal correspondence on the

§ Brock and Givner,[10] p. 784.

TABLE 1.—*Summary of Seventy-Six Cases of Alternating Strabismus* *

Case No.	Age at Onset, Yr.	Visual Acuity	Amount Tropia	Accommodative Element	Age	No. of Muscles Operated on	Immediate Postoperative Result	Retinal Correspondence	Subsequent Postoperative Findings
1	4	6/6 6/9	70 ET	Partly	9 yr.	2 horiz.	2 ET Diplopia	12 yr. NRC	3 yr. postop. 2 E; pri con 20; div 15
2	4	6/6 6/12	25 ET	Partly	.....	None	.....	14 yr. NRC Alt. suppression	.....
3	15 mo.	6/6 6/6	40 ET	None	3 yr.	4 horiz. 2 obliq.	Straight	4 yr. NRC	1 yr. postop. 5-10 E; pri con 15; div 0
4	5	6/6 6/9	50 ET	None	10 yr.	3 horiz.	3 RH	Preop. synop. ARC Postop. synop. NRC Af-im NRC	2 yr. postop. 3 RH
5	2	6/6 6/6	30 ET	Partly	6 yr.	2 horiz.	2 X	Preop. synop. ARC Af-im NRC Postop. NRC	1 yr. postop. 10 XT Synop. 20 amplitude
6	?	6/9 6/9	25 ET 10 RH	Partly	.....	None	.....	11 yr. synop. NRC	.....
7	4	6/6 6/9	70 ET	Partly	8 yr.	3 horiz.	1 ET	12 yr. synop. NRC Foveal suppression	4 yr. postop. ortho; pri con 10; div 8
8	1	6/9 6/6	85 ET	Partly	9 yr.	3 horiz.	15 ET	Preop. synop. ARC Af-im ARC 1 yr. postop. synop. ARC	1 yr. postop. 10 ET 9 LH; nice cosmetic result
9	3	6/9 6/9	5 ET 25 ET	Wholly	.....	None Bifocals	.....	Synop. NRC Worth dot SBV	Ortho; pri con 40; div 5
10	10 mo.	6/6 6/6	40 ET	Wholly	.....	None	.....	Synop. NRC Af-im NRC	Ortho with glasses; good amplitude
11	4	6/6 6/6	40 ET	Wholly	.....	None	.....	Not tested; patient deaf	Ortho with glasses
12	3 mo.	6/12 6/9	50 ET	None	2 yr. 5 yr. 6 yr.	2 horiz. 2 horiz. 2 obliq. 1 obliq.	20 ET ..... 6 ET 5 RH 5 RH 10 LH	2 mo. postop. NRC Alt. suppression	2 mo. postop. 6 ET 16 LH 5 ET 4 RH alt. hyper 1 yr. postop. 10 ET 6 RH
13	Birth or 2	6/9 6/6	65 ET 10 RH	Partly	.....	None	.....	12 yr. synop. ARC	.....
14	4	6/6 6/6	80 ET	Partly	10 yr.	3 horiz. 1 obliq.	Ortho	Preop. NRC Postop. NRC	19 mo. postop. Worth SBV SMP O; pri con 20 Did not wear glasses
15	3	6/6 6/9	50 ET	Partly	3 yr. 7 yr.	3 horiz. 2 horiz. 1 obliq.	30 ET 4 LH ..... 10 ET	7 yr. NRC	2 mo. postop. 10 ET; pri con 20; div 0
16	3	6/9 6/6	30 ET	Partly	.....	None	.....	9 yr. synop. ARC Af-im ARC and NRC	.....
17	3	6/12 6/9	30 XT	None	8 yr. 12 yr.	4 horiz. 2 horiz.	5 XT 10 XT	9 yr. NRC	2 yr. postop. 30 XT (12 yr.) 1 mo. postop. 10 XT
18	4	6/9 6/12	20 XT	None	.....	None	.....	Synop. NRC Alt. suppression	.....
19	2	6/12 6/12	24 XT	None	9 yr.	2 horiz.	10 XT	Worth dot SB Synop. NRC 55 amplitude	2 yr. postop. 0-10 X; alternates at distance; fusion at near

20	3½	6/6 6/6	25 ET	Partly	6 yr.	2 horiz.	Ortho	Synop. SMP	1 yr. postop. ortho amplitude
21	9 mo.	6/6 6/5	40 ET	None	10 yr.	4 horiz.	Ortho	Preop. synop. NRC Foveal suppression	1 mo. postop. ortho
22	Birth	6/6 6/6	80 ET	Partly	8 yr. 13 yr.	2 horiz. 2 horiz.	18 ET 8 ET	Preop. synop. ARC 13 yr. synop. ARC	3 yr. postop. 20 ET 6 wk. postop. 8 ET
23	2	6/6 6/9	35 XT	None	12 yr. 14 yr.	3 horiz. 1 horiz.	..... 3 XT	14 yr. synop. NRC and ARC Af-im NRC and ARC	14 yr. 25 XT; 15 yr. 8 XT
24	Birth	6/6 6/6	30 ET	Large	.....	None	.....	14 yr. synop. ARC Af-im NRC	With glasses; alternating hyper.
25	1	6/6 6/6	40 XT	None	7 yr.	3 horiz.	4 ET	8 yr. Worth fusion	18 mo. postop. 6 XT
26	?	6/9 6/6	10 ET 20 RH	Large	9 yr.	1 obliq.	10 RH	Preop. synop. ARC Af-im ARC 1 yr. postop. same	15 mo. postop. 10 XT 10 RH
27	3	6/6 6/6	40 ET	Wholly	.....	None	.....	Normal	Ortho with glasses
28	Birth	6/9 6/12	45 XT	Partly	.....	None	.....	13 yr. synop. NRC Af-im NRC	.....
29	1	6/12 6/12	50 XT	None	5 yr.	4 horiz.	8 XT	Preop. synop. ARC	4 mo. postop. 7 XT
30	3	6/12 6/12	20 ET	Partly	.....	None	.....	Synop. ARC	.....
31	2	6/6 6/6	75 ET	None preop.	8 yr.	4 horiz.	Straight diplopia	8 yr. synop. ARC Af-im ARC	1 mo. postop. ortho; 3 mo. postop. 1 ET 10 RH; 2 yr. postop. 25 ET 10 RH
32	9 mo.	6/6 6/5	85 ET	None	10 yr. 12 yr.	4 horiz. 2 horiz.	25 ET 12 ET	12 yr. synop. ARC Af-im ARC	Age 12 55 ET; age 13½ 20 ET
33	Birth	6/6 6/6	40 ET	Partly	15 yr.	2 horiz.	8 ET	12 synop. ARC Af-im ARC	2 mo. postop. ortho
34	4	6/6 6/6	25 ET	Partly	9 yr.	1 horiz.	XT slightly	Preop. synop. NRC Af-im NRC	2 mo. postop. ortho; 1 yr. postop. 15 et; without glasses
35	2	6/6 6/9	70 ET	None	11 yr.	3 horiz.	Ortho	11 yr. synop. NRC Af-im NRC No amplitude	2 yr. postop. ortho; no amplitude
36	2	6/9 6/9	60 ET	Partly	4 yr.	3 horiz.	5 X	1 mo. postop. synop. no SMP 3 yr. postop. synop. NRC 50 amplitude	2 yr. postop. 6 E; 3 yr. postop. 5 E
37	4	6/6 6/6	95 ET	Partly postop.	6 yr.	2 horiz.	18 ET	1 yr. postop. synop. NRC 3 yr. postop. Worth dot Alt. suppression	1 yr. postop. 4 ET; 3 yr. postop. 10 ET 3 RH
38	5	6/6 6/6	75 XT	None	.....	None	.....	Synop. NRC Af-im NRC	.....
39	7	6/5 6/9	ET	Partly	9 yr.	2 horiz.	?	13 yr. synop. NRC Af-im NRC	4 yr. postop. ortho

TABLE 1.—*Summary of Seventy-Six Cases of Alternating Strabismus* *—(Continued)

Case No.	Age at Onset, Yr.	Visual Acuity	Amount Tropia	Accommodative Element	Age	No. of Muscles Operated on	Immediate Postoperative Result	Retinal Correspondence	Subsequent Postoperative Findings
40	1	6/5 6/6	25 XT	None	6 yr. 7 yr.	2 horiz. 2 horiz.	25 XT Ortho	11 yr. synop. NRC Worth SBV	(11 yr.) 4 yr. postop. ortho; pri con 70; div 5
41	Birth	6/12 6/9	40 XT	None	9 yr.	4 horiz.	3 XT	11 yr. synop. NRC 35 amplitude Worth, suppresses OD	2 yr. postop. 6 XT
42	4	6/6 6/6	55 ET	Partly	5 yr.	1 horiz.	18 ET ac	1 mo. postop. synop. NRC Foveal suppression	1 mo. postop. ortho with glasses
43	9 mo.	6/15 6/15	35 ET 10 RH	None	11 yr.	1 horiz.	16 ET 10 RH	Preop. synop. ARC Af-im ARC	8 mo. postop. 25 ET 10 RH; 7 mo. postop. 35 ET 10 RH
44	Birth	6/6 6/6	35 ET	None	6 yr.	2 horiz. 2 obliq. Repeat R1O	8 ET	Preop. synop. ARC Af-im ARC and NRC 3 yr. postop. same	3 yr. postop. 8 ET
45	7	6/6 6/6	25 ET	None	.....	None	.....	8 yr. synop. ARC	.....
46	Birth	6/6 6/5	ET	Partly	10 yr.	2 horiz.	Ortho	5 yr. postop. synop. ARC Af-im ARC (Exo type)	5 yr. postop. 20 XT; ortho without glasses
47	5	6/6 6/6	35 ET	Partly	.....	None	.....	Synop. NRC Foveal suppression	.....
48	4	6/6 6/6	30 ET	Partly	9 yr.	2 horiz.	Ortho	Preop. synop. NRC	.....
49	3	6/9 6/9	30 ET	Partly	9 yr. 10 yr. 11 yr.	1 horiz. 3 horiz. 3 horiz.	9 ET 5 XT 5 ET	12 yr. synop. NRC and ARC Af-im NRC and ARC	1 yr. postop. 20 XT 1 yr. postop. 25 XT (age 13) 2 yr. postop. 20 XT
50	?	6/6 6/6	30 ET	None	16 yr.	2 horiz.	5 ET	Preop. synop. ARC	1 yr. postop. operate again in army
51	4	6/9 6/9	18 ET	Partly	.....	None	.....	7 yr. synop. NRC Foveal suppression	.....
52	11	6/6 6/6	65 ET	None	14 yr.	1 horiz.	ET	17 yr. synop. NRC Foveal suppression	3 yr. postop. 45 ET
53	2	6/12 6/9	50 ET	Partly	4 yr.	3 horiz.	Straight	4 yr. Worth suppression 7 yr. synop. ARC Periph. fusion	3 yr. postop. 8 ET; pri con 30; div 20
54	6 mo.	6/9 6/9	90 ET	None	.....	None	.....	11 yr. synop. ARC Af-im ARC	.....
55	1½	6/6 6/6	70 ET	Partly	11 yr. 14 yr.	1 horiz. 1 horiz.	ET 2 RH	14 yr. synop. ARC Af-im ARC 15 yr. synop. ARC	(14 yr.) 3 yr. postop. 20 ET (15 yr.) 1 yr. postop. 12 ET 3 RH
56	Birth	6/9 6/9	95 ET	Partly	6 yr. 8 yr.	2 horiz. 1 obliq.	Straight	11 yr. synop. NRC Af-im NRC Alt. suppression	(7 yr.) 1 yr. postop. alt. hyper. 11 yr. 5 LH 12 RH
57	1	6/9 6/6	60 XT	None	7 yr. 9 yr.	2 horiz. 2 horiz.	2 XT 3 XT	Preop. synop. ARC Af-im NRC 9 yr. synop. NRC	(9 yr.) 2 yr. postop. 20 XT (10 yr.) 14 mo. postop. 16 X

58	Birth	6/6 6/6	16 ET	Partly	.....	None	.....	8 yr. synop. ARC Af-im ARC	.....
59	2	6/6 6/6	70 ET	Partly	17 yr. 17 yr. 22 yr.	3 horiz. 1 horiz. 1 horiz.	20 ET 10 XT Ortho	21 yr. synop. ARC Af-im ARC	3 mo. postop. 16 ET; 4 yr. postop. 16 XT 5 RH 1 mo. postop. 0-6 ET
60	2	6/5 6/6	50 ET	Partly	.....	None	.....	10 yr. synop. ARC Af-im ARC	.....
61	1	6/12 6/9	Large ET	Partly postop.	14 mo.	.....	Unknown	12 yr. postop. synop. NRC 60 amplitude	12 yr. postop. 20 XT; ortho without + sph
62	2½	6/6 6/6	70 ET	Partly	15 yr. 15 yr.	1 horiz. 1 horiz.	5 ET Ortho	Preop. synop. ARC Postop. synop. ARC	1 mo. postop. 18 ET; 3 mo. postop. 6 ET
63	Birth	6/6 6/6	45 ET	None	16 yr.	2 horiz.	4 ET Diplopia	Preop. synop. ARC Af-im ARC	6 mo. postop. 6 ET
64	Birth	6/6 6/6	50 ET	Partly	9 yr.	2 horiz.	7 ET	Preop. synop. ARC Af-im ARC and NRC	3 mo. postop. 6 XT
65	2	6/6 6/6	ET RH	None	5 yr.	2 horiz. 1 vert.	Straight	16 yr. synop. ARC Af-im ARC	10 yr. postop. 8 XT 4 RH
66	Birth	6/6 6/6	40 ET	None	4 yr. 6 yr. 14 yr.	3 horiz. 1 horiz. 7 horiz.	10 ET Diplopia	14 yr. synop. ARC Af-im ARC	6 yr. 10 ET 30 ET; 14 yr. 95 XT; 18 yr. (17 mo. postop.) 6 XT
67	Birth	6/6 6/6	ET	None	6 yr. 14 yr. 17 yr.	1 horiz. 1 horiz. 1 horiz.	Straight XT Straight	17 yr. synop. ARC Af-im ARC	7 yr. started to diverge; 14 yr. 70 XT postop. 35 XT; 19 yr. (2 yr.; postop.) 4 XT
68	5	6/6 6/12	14 ET	Wholly	.....	None	.....	15 yr. synop. NRC Af-im NRC Amplitude	15 yr. 5 E with glasses
69	?	6/9 6/9	30 XT	Partly	9 yr.	1 horiz.	5 E	8 yr. synop. NRC 10 yr. worth SBV	18 mo. postop. 16 XT; ortho with + sph cut
70	3	6/6 6/5	35 XT 15 LH	None	34 yr.	2 horiz. 1 vert.	3 X 14 LH	34 yr. synop. ARC Af-im ARC	19 mo. postop. 10 XT 14 LH
71	5	6/9 6/12	50 ET	Partly	8 yr.	2 horiz.	5 ET	Preop. synop. ARC Af-im ARC	1 mo. postop. 8 ET
72	7	6/6 6/9	85 ET	Partly	.....	None	.....	40 yr. Af-im ARC	.....
73	Birth	6/6 6/9	15 ET	None	.....	None	.....	8 yr. synop. ARC Periph. fusion	.....
74	4	6/12 6/6	55 ET	Partly	.....	None	.....	43 yr. synop. ARC Af-im ARC	.....
75	2	6/6 6/6	35 ET	Partly	9 yr.	2 horiz.	Straight	Preop. synop. ARC Af-im ARC	.....
76	?	6/6 6/9	12 ET	None	11 yr.	1 horiz.	Straight diplopia	Preop. synop. ARC Af-im ARC	1 mo. postop. 3 ET; 1 yr. postop. 12 ET

* Worth dot SBV indicates single binocular vision on Worth four-dot test; SMP, simultaneous macular perception; Pri con, prism convergence; NRC, normal retinal correspondence; ARC, abnormal retinal correspondence; synop., synoptophore; and Af-im, after-image.

synoptophore and in the after-image test. It is of interest to note that all 22 patients showing anomalous correspondence with after-images gave the same findings on the synoptophore, and 4 of these showed a vertical separation of the after-images.

EFFECT OF ANOMALOUS CORRESPONDENCE ON POSTOPERATIVE RESULTS

Much has been written regarding the effect of anomalous correspondence on postoperative results. The opinions of various authors are conflicting. Lyle || states:

TABLE 2.—*Incidence of Anomalous Correspondence in Relation to Age of Onset and Type of Squint for Seventy-Six Cases*

Age of Onset	Up to Age 3			Age 3 or Over			Unknown	
Retinal Correspondence	Normal	Abnormal	Equivocal	Normal	Abnormal	Equivocal	Normal	Abnormal
Esotropia								
Entirely accommodative	10	..	..	9, 11, 27, 68	..	..	..	..
Partly accommodative	36, 56 61	8, 13, 22, 31, 33, 46, 53, 55, 58, 59, 60, 62, 75	24, 5 64	1, 2, 7, 14, 15, 20, 34, 37, 39, 42, 47, 48, 51	30, 71, 72, 74	16, 49	6	26
Nonaccommodative	3, 12, 21, 35	32, 43, 54, 63, 65, 66, 67, 73	44	52	45	4		50, 76
Total no. cases	8 24%	21 64%	4 12%	18 69%	5 20%	3 11%	1	3
Exotropia								
Intermittent	19, 28 40	25		18			69	
Not intermittent	41	29	23, 57	17,38	70			
Total no. cases	4	2	2	3	1	..	1	

TABLE 3.—*Analysis of Forty-One Cases Showing Anomalous Correspondence*

Testing Method and Findings	Case No.	Total No. of Cases
ARC on synoptophore and ARC on after-image	8, 31, 33, 46, 55, 58, 59, 60, 75, 32, 43, 54, 63, 65, 66, 67, 71, 72, 74, 70, 76, 26	22
ARC on synoptophore and NRC on after-image	4, 5, 24, 57	4
ARC and NRC on synoptophore and/or ARC and NRC on after-image	16, 23, 44, 49, 64	5
ARC on synoptophore (not tested or unsatisfactory after-images)	13, 22, 53, 62, 73, 25, 29, 30, 45, 50	10
Vertical separation of after-images	26, 31, 65, 70	4

If the eye after operation is neither divergent nor convergent, then its position may be considered to be the outcome of two opposing reflexes, the one due to secondary correspondence tending to make the eye reassume its convergent position, and the other due to normal correspondence opposing this and keeping the eye in a straight position.

Jackson [11] agrees with Lyle that anomalous correspondence may affect the final position of the eyes and states:

There is the possibility that after an imperfect operation where some degree of squint still remains, the eye may deviate again, in order to bring back into use the old non-corresponding points.

|| Lyle,[4] p. 198.

¶ Lyle and Jackson,[11] p. 57.

She cites a case in which the preoperative angle of convergence was 15 degrees, with a 15 degree angle of anomaly (harmonious anomalous correspondence). Two weeks after operation the objective angle was 2 degrees, but six weeks later the objective angle was again back to the original 15 degrees of convergence and the angle of anomaly was still 15 degrees. Jackson goes on to say that there is some danger of the visual axes deviating postoperatively in order to regain binocular vision if the anomalous correspondence is well established; she says that if this should occur, occlusion should be carried out at once.

Others who feel that anomalous correspondence will hinder a good operative result are Mildred Smith, Dicke, and Pugh. Miss Smith [12] reports a series of cases in which the eyes remained straight in only 4 out of 30 with anomalous correspondence, as compared with 17 out of 19 with normal correspondence. Dicke [13] also felt that anomalous correspondence does alter the operative result and reported a series of cases in which surgical correction was obtained in 85% with normal correspondence, as compared with only 69% with anomalous correspondence. Finally, Pugh [6] states that a patient with anomalous correspondence whose eyes are straightened may follow one of three courses: (1) recover normal retinal correspondence and fuse bifoveally; (2) readapt his projection, tending to recover some of the original deviation, or (3) retain his false projection and be sufficiently troubled by paradoxical diplopia to revert to the original squint in order to overcome this symptom.

Opposed to the foregoing views are Prangen,[14] Burian,[15] Travers,[16] and Scobee,[17] all of whom feel that the presence or absence of anomalous correspondence has little effect on the surgical result. Prangen [14] states that only patients with extreme amblyopia and eccentric fixation tend to return to the original deviation after surgery. Scobee # disagrees with Lyle and Jackson's explanation that a return to the original angle of esotropia is due to anomalous correspondence. From his experience with "the few patients where this chain of events has occurred," he states:

> A second operation has invariably revealed contracting bands of scar tissue between the new [recessed] insertion of the medial rectus and its former insertion. . . . I do not believe that anomalous correspondence per se which persists postoperatively will effect the return of an esotropia following an apparently successful operation. I believe that one can usually find, and prove, that some other cause was responsible for the recurrence. . . . Swan (1945) demonstrated that anomalous correspondence tends to adapt itself to the angle of the deviation. He reported a series of 100 patients corrected surgically to within a few degrees of the position of zero deviation. They had no other treatment except surgery for their anomalous correspondence. Postoperatively, the correspondence was found to have adjusted itself to the new angle of residual deviation in the majority of the cases.

Finally, Burian [18] states that he has never found abnormal correspondence to be a serious handicap in obtaining a good operative result and that the cosmetic result is just as good in patients with normal as in patients with abnormal correspondence. If the result was not satisfactory, he could almost always detect a mechanical reason for it.

None of these authors state specifically whether their patients had good visual acuity in each eye, by what method their retinal correspondence was determined, or how long their patients were followed postoperatively.

In the present series, patients were selected who had good vision in each eye, and hence should be good candidates for postoperative single binocular vision. An

Scobee,[17] p. 367.

attempt was made to determine how deeply rooted the retinal correspondence was, and, finally, the patients were followed, when possible, for more than one year. It was felt that by the end of one year one could generally predict the outcome in a squint case by knowing whether the deviation was stable or still drifting toward a convergent or divergent position.

Table 4 shows the postoperative results in 53 cases. In general, the patients were kept in the hospital and reoperated upon if necessary. They were sent home when the alignment was considered satisfactory. It can be seen that 23 cases showed normal retinal correspondence, 2 of which were operative failures. In one (Case 52) failure was due to insufficient surgery (the patient signed his release from the hospital before a second operation could be performed). In the other (Case 17) the patient had an alternating exotropia with profound alternate foveal suppression and drifted back to the original angle of squint after two years. If Case 52 is omitted as a failure, a good result (functional or cosmetic) was obtained in 96% of the cases with normal correspondence. An important point concerning the cases with normal correspondence is that the surgical alignment which was obtained before the patient left the hospital was maintained in all cases except the one failure (Case 17). Only

TABLE 4.—*Evaluation of Surgical Results in Fifty-Three Cases of Alternating Strabismus*

Normal retinal correspondence	Functional (phoria)		1, 3, 7, 14, 20, 36, 40, 56, 69	9	41% } 96%
	Good cosmetic result (under 10° deviation)		12, 15, 19, 21, 34, 35, 37, 39, 41, 42, 48, 61	12	55% }
	Failure (over 10° deviation)		17, (52)	2	4%
Abnormal retinal correspondence	Good cosmetic result		8, 22, 25, 26, 29, 33, 53, 59, 62, 63, 65, 70, 71, 75	14	61%
	Failures	Return to original angle	43, 76	2	} 39%
		Partial return to original angle	31, 32, 50, 55	4	
		Overcorrection	46, 66, 67	3	
Equivocal retinal correspondence	Good cosmetic result		4, 5, 44, 64	4	
	Failure		23, 49, 57	3	

4 of the 23 patients had to return for further surgery. Two (Cases 12 and 56) had a postoperative double hyperphoria and had only oblique muscle surgery at the second hospitalization. The third (Case 15), with an accommodative element, did not wear his glasses for two years and required a second operation. The fourth (Case 40) did not have adequate correction when discharged and required subsequent surgery, as expected.

Of the 23 patients with abnormal correspondence, 61% (14 cases) had good cosmetic results without repeated hospitalization or excessive amounts of surgery. The other 39% (9 patients with esotropia), who had satisfactory cosmetic results at the time of discharge from the hospital, later showed either a partial or a complete return to the original angle of squint, or developed a severe postoperative divergence. Of these nine patients, four had subsequent surgery which gave them satisfactory cosmetic results, although in two of the overcorrections (Case 66 and 67) the surgery had to be repeated several times.

A point to be emphasized is that all 23 cases showing anomalous correspondence still had it postoperatively, regardless of whether the operative result was good or bad. In none of these cases were after-images changed from abnormal to normal by surgery.

The three cases of overcorrection (Cases 46, 66, and 67) are worthy of discussion because they showed some interesting and common features. All three patients

were born with an esotropia, and following their first surgery (after the age of 4) their eyes remained straight for about one year, then began to diverge. When they were tested later in life, they showed uncrossed (homonymous) after-images, such as are seen in exotropia with anomalous correspondence. This would indicate that the anomalous correspondence must have changed from an esotropic to an exotropic type after surgery. It is highly probable that these patients were born with a deeply rooted anomalous correspondence, as has also been suggested by Adler [7] and Brock and Givner,[10] and were unable to develop normal correspondence, even though the eyes were placed surgically in a good position to encourage the development of normal correspondence. If these patients were born with normal correspondence, then certainly the surgical alignment should have been maintained, as it was in all the other patients with normal correspondence. It is very difficult to believe that if these patients had been born with an esotropia and normal correspondence, they would show exotropia and anomalous correspondence on after-image following surgery. Therefore, one cannot help feeling that in these three patients the deeply rooted anomalous correspondence or the inability to develop normal correspondence was present at birth and played an important role in causing the marked postoperative divergence. (These three patients should be compared with three others who showed a slight postoperative exotropia (Cases 26, 59, and 65) but who still maintained after-images of the esotropic type and a satisfactory cosmetic result.)

In the final group, with equivocal retinal correspondence, there were four patients with good results and three with poor results. Of the four with good results, two (Cases 4 and 5) showed anomalous correspondence on the synoptophore and normal correspondence on the after-image test. These two patients were not born with strabismus, and after surgery they showed normal correspondence on all tests. The other two patients (Cases 44 and 64) showed both normal and abnormal after-images at different times prior to operation. After surgery the findings were still equivocal. In the three patients with poor results, two had exotropias which drifted back toward the original angle of squint but which were made cosmetically satisfactory by subsequent surgery. The other patient (Case 49) was originally esotropic and the eyes became divergent postoperatively with a surgical paresis of the medial rectus muscles. Hence, the unsatisfactory result was more likely due to the generous surgery than to the influence of retinal correspondence.

The following illustrative cases show the harmful influence of abnormal binocular reflexes on operative results.

CASE 1.—R. L. had had an alternating esotropia of 75 △ since 2 years of age. His vision was 6/6 in each eye. There was no apparent accommodative element preoperatively, though there was some postoperatively. His refraction was +1.50 D. sph. in both eyes. At age 8 he had a recession of the medial rectus and a resection of the lateral rectus muscles of the right eye. Since this corrected only half the strabismus, the same procedure was performed on the left eye five days later. After the second operation, his eyes were perfectly straight. When the dressings were removed, the patient complained of a troublesome postoperative paradoxical diplopia. He was reassured that the diplopia would disappear. When he was examined the following day, his diplopia had disappeared but his esotropia had returned in as bad a form as it was preoperatively. He then wore an occluder for a day, and his eyes became straight. Whenever the occluder was removed, his diplopia would return and his eyes would turn in again until the diplopia disappeared. When occluded, his eyes would straighten again. He was sent home with instructions to use alternate occlusion, and in the meantime was given orthoptic treatment to stimulate the two foveas simultaneously. The orthoptic training

was unsuccessful and was discontinued after one month, but the alternate occlusion was continued. Three months later the patient lost interest and stopped coming to the clinic. At this time he showed 12△ of esotropia. Two years later he was asked to come in for examination. At this time he showed 25△ of esotropia. This could be reduced to 16△ if he wore his +1.50 D. spheres. Both the synoptophore and the after-image test showed anomalous correspondence immediately postoperatively and also two years later. There is no doubt that the abnormal binocular reflexes played an important part in the partial return of this patient's esotropia. This was shown dramatically by the immediate postoperative diplopia, which the patient unconsciously would overcome by turning his eyes in. Yet with occlusion, his eyes would straighten to the position of surgical alignment. The fact that the residual esotropia two years later was not worse than it was can probably be attributed to the immediate postoperative alternate occlusion.

Case 2.—J. H., age 9 years, had an alternating esotropia of 12△. Since this was not a cosmetic blemish, the parents were unable to give an accurate history of onset. Vision was 6/6 and 6/9. His refractive error was +1.25 D. sph. in each eye, and there was no accommodative element. Both synoptophore and after-image test showed a deeply rooted anomalous correspondence. The patient was given a 6 △ base-out prism over each eye to see whether both foveas could be stimulated optically. After he had worn these one month, his objective angle increased to 24 D., showing the strength of the abnormal binocular reflexes. When the prisms were removed, the objective angle returned to 12 D., and when the prisms were worn, the angle increased to 24 D. At age 11 a 6 mm. resection of the left lateral rectus muscle was performed. One week postoperatively, when dressings were removed, there was a trace of exotropia on cover test, and the patient had paradoxical diplopia. Within two days the diplopia was gone and the 12△ of esotropia had returned. The patient was sent home on alternate occlusion therapy. One month later the patient was found to be orthophoric on cover test. The occlusion was stopped for three weeks, and 12△ of esotropia returned. The patient again had occlusion for one month, after which he showed only 4△ of esotropia.

This case also shows the strength of abnormal binocular reflexes in that prisms increased the angle of squint in order to maintain the angle of anomaly. Surgical alignment was maintained only as long as the abnormal binocular reflexes were eliminated by occlusion.

Case 3.—R. S. was born with an alternating esotropia of 40 △. Her vision was 6/6 in each eye, and there was no accommodative element. At age 4 she had a recession of the left medial rectus and a tuck of the left lateral rectus muscles. On discharge from the hospital she had 20△ of esotropia. One month later she had a Worth advancement of the right lateral rectus muscle, after which her eyes were straight. Two years later, at age 6, she showed 30△ of esotropia; a Worth advancement of the left lateral rectus muscle was therefore performed, after which her eyes were again straight. Eight years later, at age 14, she showed 95△ of postoperative exotropia. From age 14 to 15 the horizontal muscles were operated upon seven times in order to correct the postoperative divergence. After each operation she had a troublesome postoperative diplopia and her eyes would start to diverge again. After the last surgery she had no deviation at near and 6 △ of exotropia at distance. This correction has been maintained for two years. This girl's after-images showed an anomalous correspondence of the exotropic type, i. e., uncrossed, or homonymous. It would seem reasonable to assume that she had anomalous correspondence from birth, since she was born with esotropia. Then, after repeated surgery for the continuously returning esotropia, her eyes remained straight for a short time, only to become severely divergent with an adapted anomalous correspondence.

Certainly, this patient's abnormal binocular reflexes must have been a factor in her repeated operative failures, since she was given many opportunities surgically to develop normal binocular reflexes, only to reject them repeatedly. As discussed previously in this paper, one cannot help feeling that in this case the patient was

born with anomalous correspondence which could adapt itself easily to esotropia or exotropia, but she was unable to develop normal correspondence when given the opportunity.

CASE 4.—M. P. was born with an alternating esotropia. Her vision was 6/6 in each eye. At age 6 she had a tuck of a lateral rectus muscle. After this her eyes remained straight for one year; then by age 14 she had 70△ of exotropia. This was corrected cosmetically by two subsequent operations. Her after-images showed an anomalous correspondence of the exotropic type.

This case is similar to the previous one except that a simple tuck of one lateral rectus muscle easily threw the patient into a severe divergence, suggesting a very adaptable type of anomalous correspondence and a lack of desire for normal correspondence.

SUMMARY

1. Approximately 50% of unselected squint patients showed either equal vision or vision within two lines' difference on the Snellen chart.

2. Anomalous retinal correspondence was present in 64% of cases of alternating esotropias in which onset occurred before 3 years of age. It was present in 20% of the cases in which onset occurred after 3 years of age. All cases showing anomalous correspondence on the after-image test gave the same findings on the synoptophore test. A few cases showed anomalous correspondence on the synoptophore but normal correspondence on the after-image test. There were no cases which showed normal correspondence on the synoptophore and abnormal correspondence on the after-image test. Four cases showed a vertical separation of the after-image.

3. Good surgical results were obtained in 96% of the cases showing normal retinal correspondence. Furthermore, the surgical alignment was maintained in all these cases. These good results were considered functional in 9 cases (41%), since they were phorias and showed some amplitude of fusion, and were considered cosmetic in 12 cases (55%), since they were tropias, even though some of them showed amplitudes of fusion on the synoptophore.

4. Good surgical results were obtained and maintained in 61% of cases showing abnormal retinal correspondence. In the other 39% good surgical alignment was not maintained. The squint either returned partially or completely to the original angle of deviation or became markedly divergent. Satisfactory cosmetic results were later obtained by further or repeated surgery (under 10 degrees or 20 △ of deviation was considered to be a satisfactory cosmetic result).

5. In this series, there were no cases in which after-images were changed from abnormal to normal by surgery. However, in the three failures with marked postoperative divergence, the after-images were presumably changed from an esotropic to an exotropic type of anomalous correspondence. These three patients were born with esotropia and hence the cases suggest the possibility of being born with anomalous correspondence.

6. There were only 3 cases (two with esotropia, Cases 4 and 5, and one with exotropia, Case 57) out of the 41 in which abnormal correspondence changed to normal correspondence after surgery. In these cases there were normal after-images preoperatively, although the synoptophore showed an abnormal correspondence.

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PERIODIC UNILATERAL EXOPHTHALMOS

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EXOPHTHALMOS, with or without endocrine dysfunction, is an interesting disease manifestation which is poorly understood. Research on the association of endocrine dysfunction and exophthalmos has been stimulated by the advent of endocrine extracts, but, although much has been learned, the exact relationship is still not known. A unique case of rhythmical periodic unilateral exophthalmos of three years' duration is presented. The patient has been observed over a period of one and one-half years; extensive laboratory data were obtained, and clinical investigations with endocrine extracts were made. A brief résumé of some of the pertinent recent research on endocrine relationship to exophthalmos is included. A review of the medical literature has not revealed a similar case.

REPORT OF A CASE

A. History.—G. N., a 45-year-old white male veteran, was admitted to Veterans Administration Hospital, Cleveland, on Aug. 7, 1952, with the chief complaint of periodic edema of the left eyelids, of two years' duration. The patient was born in Pennsylvania and lived in Pennsylvania and New York until 1949, when he moved to Ohio. He spent approximately 14 years on active duty in the United States Naval Reserve and served in North Africa in 1942 and 1943, and again in 1950 and 1951. He had had the usual childhood diseases without sequelae and had enjoyed excellent health until the onset of the present illness.

In October, 1950, the patient developed nausea, vomiting, diarrhea, and low-grade fever. He was hospitalized at the Naval Hospital in Portsmouth, Va. His symptoms responded to conservative treatment in five to seven days. During the hospitalization the attending physician noted that there was swelling and dusky discoloration of the left eyelids. The patient had not previously been aware of the existence of this condition. The edema of the left lids cleared spontaneously, and the patient was discharged from the Portsmouth Naval Hospital to full naval duty. No diagnosis was made. Since his discharge from the hospital, the patient has noted that the swelling and dusky discoloration of the left eyelids recur at approximately monthly intervals. He remained subjectively asymptomatic until January, 1951, at which time the attacks became so severe that the left eye swelled shut and he was aware of episodes of diplopia on looking in other than the primary position. The patient continued on full naval duty until August, 1951, at which time he was to be discharged from the naval service. Physical examination, prior to separation from the service, revealed swelling of his left eyelids, and he was referred to the Naval Hospital, Chelsea, Mass., for evaluation of this condition. Examination at the Chelsea Naval

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Hospital revealed edema of the left lids, with a mass occupying the medial one-third of the lower left lid. Biopsy of this mass was attempted, and histological examination of the tissue removed was reported as normal. The surgeon stated that no mass could be found at operation. The remainder of the diagnostic examination was negative, and the patient was discharged from the hospital and the naval service with a diagnosis of angioneurotic edema, etiology undetermined, with a service-connected disability of 10%.

Since discharge from the naval service, the patient has continued to have attacks of edema of the left lids at approximately monthly intervals. He has been seen by several physicians for the purposes of evaluation and rating, and a wide variety of diagnoses have been made, including angioneurotic edema, allergy, and conjunctivitis. No record of an exophthalmic reading was noted in his previous medical records, nor was any mention made of restricted ocular motility. All the examiners agreed on the presence of left periorbital edema with a dusky discoloration of the eyelids. On Aug. 7, 1952, the patient was admitted to Veterans Administration Hospital, Cleveland, for evaluation.

B. Physical Examination.—At the time of admission, on Aug. 7, the patient was just past the peak of an attack. Physical examination revealed a well-developed, moderately obese, bald white man with no physical abnormalities other than those of the left eye. Eye examination revealed the uncorrected vision to be 20/20 and J-1 bilaterally. The right eye was found to

Time Interval Between Attacks of Exophthalmos When Untreated

Date of Onset	Time Interval Between Attacks, Days
Aug. 2	..
Aug. 25	23
Sept. 25	31
Oct. 31	36
Dec. 4	34
Jan. 2	29
Average	31

be entirely normal. There was a dusky discoloration of the left upper and lower lids with marked edematous swelling. A discrete, firm, freely movable, subcutaneous nodule, approximately 1 by 0.5 cm. in size, was palpable in the medial one-half of the left lower lid. There was mild dilatation of the bulbar conjunctival vessels, but no conjunctival edema. The left eye appeared proptosed, and measurements with the Hertel exophthalmometer, with a central setting of 100 mm., was 15 mm. O.D. and 21 mm. O.S. The proptosis was not reducible with digital pressure. There was no eccentric displacement of the eye. The patient was essentially orthophoric. There was limitation of motion of the left eye in the extreme positions of gaze with diplopia. Tactile tension was normal. The pupils were round and equal and reacted normally to light and in accommodation. Ophthalmoscopic examination, with mydriasis, revealed the retinal vasculature to be normal. Peripheral and central visual fields were normal.

C. Course of Attacks.—Since admission to the hospital, the patient has been observed through six attacks of periodic unilateral exophthalmos, which were untreated. The time interval between the onset of attacks has varied from 23 to 36 days, with a mean of 31 days between attacks (Table).

The attacks have all followed the same general pattern, and a typical sequence of objective changes is illustrated in Figures 1 through 5. During the quiescent phase, the patient was completely asymptomatic. There was a slight residual fulness beneath the left eye, and exophthalmic measurements revealed 3 mm. more proptosis of the left eye than of the right eye (Fig. 1).

The onset of an attack was characterized by the gradual development of periorbital edema and proptosis on the left. By the third day after onset edematous swelling of the left eyelids was well established. There was slight bulbar conjunctival edema with dilatation of vessels over the temporal half of the globe. A subcutaneous nodule, approximately 1 by 0.5 cm. in size,

was palpable in the medial one-half of the left lower lid. Exophthalmic measurements revealed an increase in the proptosis of the left eye, with 6 mm. difference in the measurements of the two eyes (Fig. 2).

The attacks reached their peak in five to seven days. There was marked edematous swelling of the left eyelids, as well as moderate conjunctival edema and dilatation of bulbar conjunctival vessels, especially on the temporal portion of the globe (Fig. 3).

There was variation in the intensity of the attacks, and sometimes the left eye would be completely closed, with edematous conjunctiva herniating between the lids (Fig. 4). The limitation of motion of the left globe was marked, and the patient had diplopia in all except the primary position of gaze. The subcutaneous nodule in the medial one-half of the left lower lid was dis-

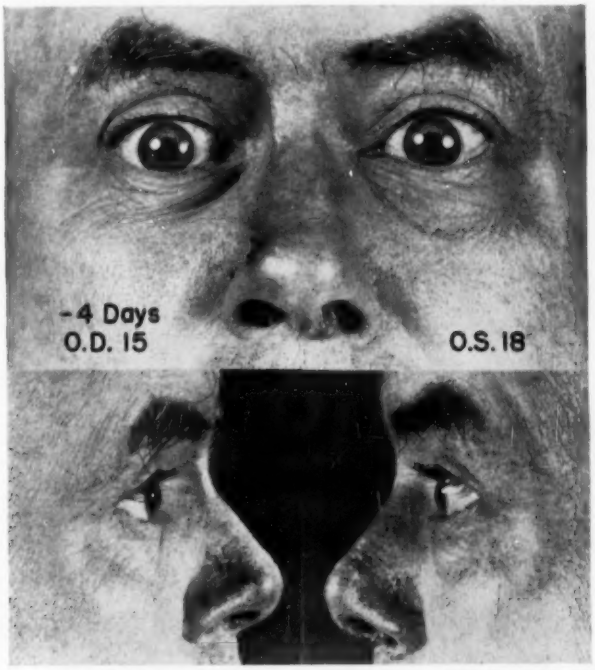

Fig 1 (G. N., Aug. 21, 1952).—Approximately four days prior to the onset of an attack, when the condition was quiescent. There was a slight residual fullness beneath the left eye and slight proptosis of the left eye. Exophthalmic measurements were O.D. 15 mm. and O.S. 18 mm. The patient was completely asymptomatic at this time.

crete. A swelling was usually apparent at the medial border of the left upper lid. This swelling is commonly seen in irreducible forms of exophthalmos and has been attributed by Rundle and Wilson,[1] Dobyns,[2] and others to a herniation of the retro-orbital fat through a weakness of the supporting structures of the globe. The proptosis of the left eye was very pronounced, and exophthalmic measurements revealed 6.5 to 7 mm. difference in the measurements of the two eyes.

During the 5 to 7 days following the peak of an attack, the objective and subjective symptoms gradually regressed (Fig. 5), and by the 14th day after the onset of symptoms the condition had subsided to normal.

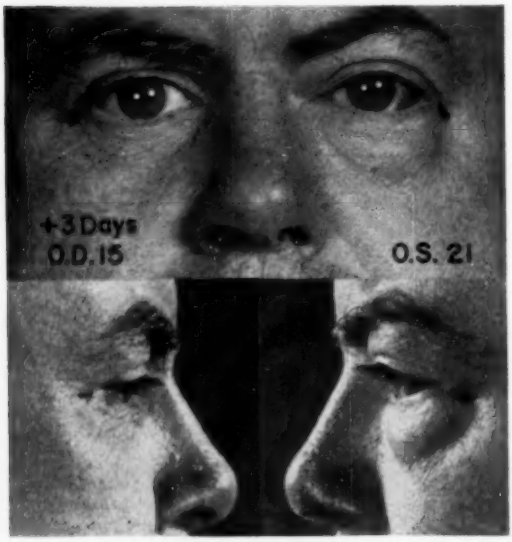

Fig. 2 (G. N., Aug. 27, 1952).—Approximately three days after the onset of subjective and objective symptoms. Edematous swelling of the left eyelids and slight conjunctival edema were evident. Exophthalmic measurements were O.D. 15 mm. and O.S. 21 mm.

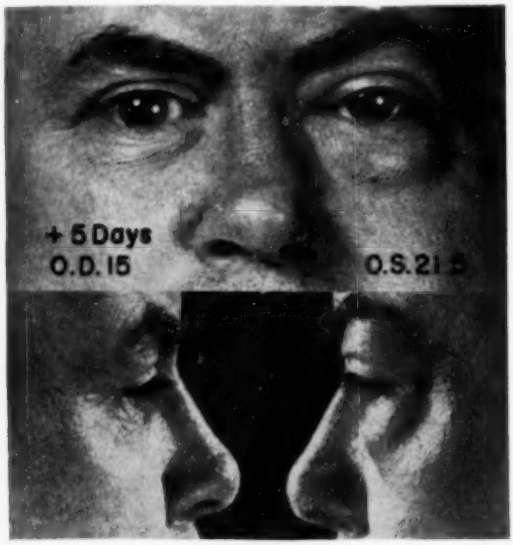

Fig. 3 (G. N., Aug. 29, 1952).—Approximately five days after the onset of symptoms, illustrating the peak of this attack. Marked edematous swelling of the left eyelids and conjunctival chemosis were present. Proptosis of the left eye was marked. Exophthalmic measurements were O.D. 15 mm. and O.S. 21.5 mm.

SUMMARY OF DIAGNOSTIC STUDIES

A. Routine Studies.—Routine urinalysis and serologic studies were negative. The white blood cell count varied from 5,500 to 8,700, but there was no correlation with attacks. The differential count revealed 10 to 20% eosinophiles. X-rays of the chest, skull, orbits, paranasal sinuses, and teeth were normal. Examinations of the ears, nose, throat, and teeth were negative. Allergy evaluation and skin tests were noncontributory. The histamine sensitivity reaction was negative. Daily resting blood pressures, weights, and fluid intake and output studies showed no significant alteration during an attack. Repeated blood smears for parasites were negative. Precipitin tests for Trichinella and Echinococcus were negative. Purged stools revealed the present of Endamoeba histolytica, and complement fixation tests for Endamoeba were 2+. This infection was

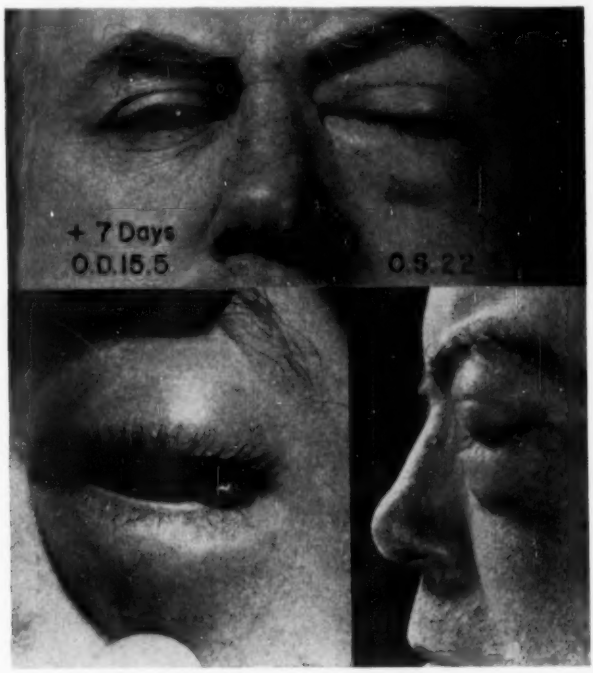

Fig. 4 (G. N., Oct. 1, 1952).—Approximately seven days after the onset of symptoms. These photographs, taken during another attack, illustrate the degree of incapacity which this patient has suffered. When the left eye was forceably opened, chemotic conjunctiva herniated through the palpebral fissure. On the following day exophthalmic measurements were obtained and were 15.5 mm. O.D. and 22.5 mm. O.S.

successfully treated, and although subsequent purged stools were negative, no alterations occurred in the attacks of periodic exophthalmos. Repeated visual field examinations were normal. The intraocular tension remained well below 30 mm. Hg Schiøtz, although the tension in the left eye was 4 or 5 mm. of Hg higher than the tension in the right eye during an attack.

B. Assay for Exophthalmic Factor.—Minnow assay for exophthalmic factor was done by Dr. Brown Dobyns, City Hospital, Cleveland, and was negative.

C. Iodine Uptake Studies.—Radioactive iodine uptake studies were done before, during, and after an attack and were normal. A summary of these studies follows.

Sept. 2, 1952: The patient was given 50μc of radioactive iodine, with 17% uptake in 24 hours.

This was approximately nine days after the onset of symptoms and about four days past the peak of an attack.

Sept. 23: The patient was given 50μc of radioactive iodine, with 20% uptake in 24 hours. This was during the quiescent phase, being 30 days after the onset of the preceding attack and 2 days prior to the onset of symptoms.

Sept. 29: The patient was given 50μc of radioactive iodine, with 27% uptake in 24 hours. This was five days after the onset of an attack and was approximately at the peak of an attack.

D. Variation in Eosinophilia.—Eosinophile counts were done repeatedly on this patient and revealed a mean of 600 to 800 circulating eosinophiles per cubic millimeter during remissions, in contrast to a normal level of 150 to 200 eosinophiles per cubic millimeter. The eosinophile count increased dramatically during an attack and paralleled the degree of development of exophthalmos. At the peak of an attack of exophthalmos, the circulating eosinophiles reached a level of 1,000 to 1,200 per cubic millimeter, then gradually returned to 600 to 800 per cubic millimeter.

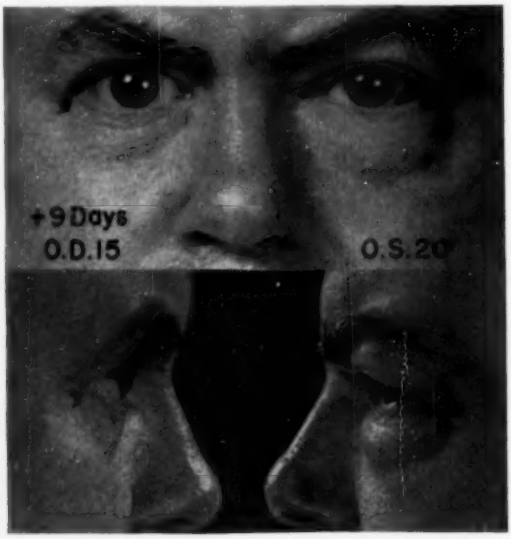

Fig. 5 (G. N., Sept. 2, 1952).—Approximately nine days after the onset of symptoms. Resolution of the attack is in progress. Objective and subjective symptoms have regressed. Exophthalmic measurements were 15 mm. O.D. and 20 mm. O.S. During the next five days the symptoms continued to regress and the disease became quiescent, as in Figure 3.

The variation in circulating eosinophiles, occurring during two attacks, is illustrated in Figure 6.

E. Variation in Exophthalmic Measurements.—Exophthalmic measurements were taken daily during hospitalization and at follow-up examinations. A Hertel exophthalmometer was used with a central setting of 100 mm. These studies revealed that the degree of proptosis of the left eye gradually increased from the established normal to reach a peak in five to seven days and then gradually regressed during the next five to seven days to the same normal reading. At the peak of an attack there was approximately 7 mm. difference between the exophthalmic measurements of the two eyes, with a residual difference of 3 mm. during remission. Two typical attacks are illustrated in Figure 7.

F. Variation in 17-Ketosteroid Excretion.—The 17-ketosteroid excretion of the patient was followed during the course of two attacks. The number of these determinations which it was possible to obtain was limited; however, the values indicated a trend toward decreased 17-ketosteroid excretion during the course of an attack (Fig. 8).

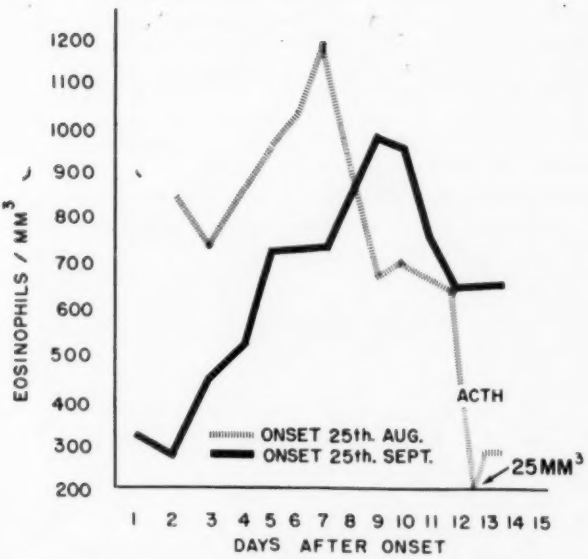

Fig. 6.—Variation in circulating eosinophiles per cubic millimeter of blood during two typical attacks, and the effect of ACTH therapy.

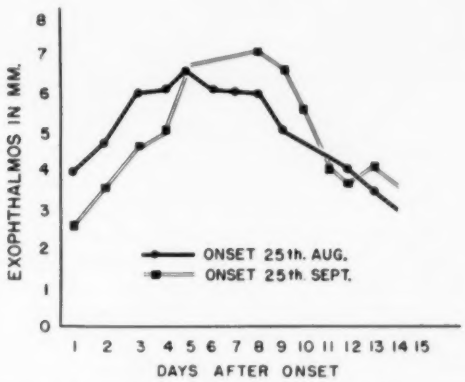

Fig. 7.—The difference, expressed in millimeters, between the exophthalmometric measurements of the two eyes during the course of two typical attacks.

G. Biopsy of the Orbicularis Muscle.—A biopsy of the nodule in the left lower lid was performed on Nov. 5, 1952. Anesthesia was obtained by injecting 2% procaine with epinephrine in a 2 cm. circle surrounding the nodule. The nodule had been discrete, but after the injection of the anesthetic it was no longer distinctly palpable. This may have been the result of the vasoconstrictor effect of the epinephrine. An incision was made through the skin, paralleling the lid margin, directly over the noted position of the nodule. The orbicularis muscle was found to be grossly thickened, an estimated four times its normal thickness, and appeared paler than normal. There was thickening of the connective tissue of the muscle sheath. A generous biopsy specimen was taken. The nodule has not reappeared since surgical excision, supporting the surgical impression that the nodule was the result of orbicularis thickening. A photomicrograph of a representative section is illustrated in Figure 9.

Microscopic examination revealed skeletal muscle, which was covered on one surface by a heavy band of moderately dense connective tissue with occasional skeletal muscle fibers. These fibers were considerably smaller than those constituting the main muscle mass. Throughout the connective tissue and muscle, the vascular spaces were unusually prominent and were filled with

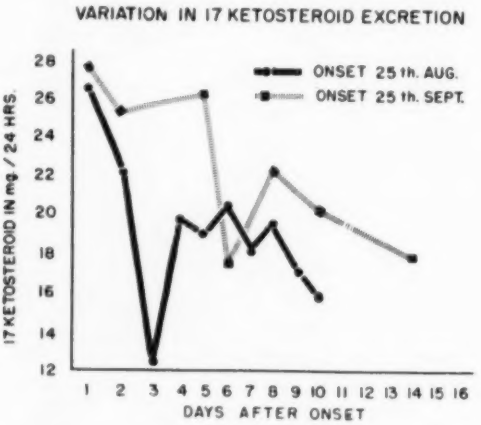

Fig. 8.—Variation in 17-ketosteroid excretion during two attacks, expressed in milligrams per 24 hours.

bright pink amorphous material. Many of the vessels were surrounded by an infiltration of cells, of three principal types. One type was a large mononuclear cell, having a considerable amount of poorly defined cytoplasm and an oval, or somewhat irregular, nucleus with fairly granular chromatin. There was also a small mononuclear cell having little or no identifiable cytoplasm and a round dark nucleus without visible intranuclear structure. The third component was a polymorphonuclear or mononuclear cell, containing numerous large eosinophilic granules in the cytoplasm. In some of the polymorphonuclear cells the granularity was indistinct, suggesting the possibility that some of the cells were neutrophiles. In many of the vessels both eosinophiles and neutrophiles were prominent, but they were arranged almost exclusively on the endothelial surface. The blood vessel walls were normal. There was focal hyalinization in the muscle, which was considered a possible artifact; with the exception of those muscle fibers in the connective tissue sheath, no definite alteration in the muscle was identified. Clinically there was marked edema and congestion of the lids, but edematous changes were not pronounced microscopically. The pathologic diagnosis was perimysial fibrosis with hyperemia and chronic perivascular inflammation of skeletal muscle. Biopsies of the gastrocnemius and deltoid muscles were obtained on this patient during an attack and were normal.

A. Corticotropin (Adrenocorticotropic Hormone).—Corticotropin was administered to the patient to determine the adrenocortical response; 25 mg. of corticotropin was given in a slow intravenous drip over an eight-hour period. This produced a rapid reduction of circulating eosinophiles, from 650 to 25 per cubic millimeter, which is considered a normal response. The number of circulating eosinophiles gradually rose again to 250 per cubic millimeter within 24 hours and remained at this level until the onset of the next attack (Fig. 6). This is the explanation of the relatively normal level of circulating eosinophiles occurring at the onset of the attack of exophthalmos beginning Sept. 25, 1952 (Fig. 6).

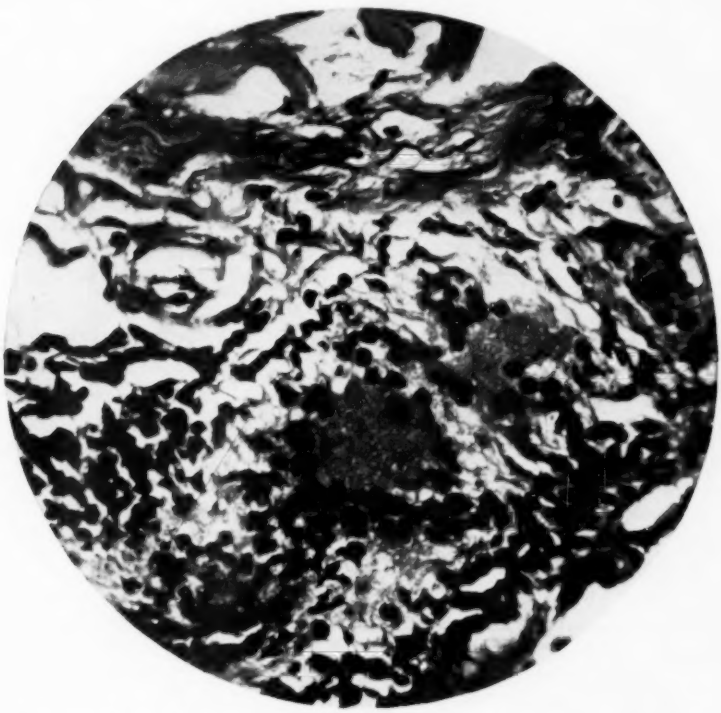

Fig. 9.—Biopsy of the orbicularis muscle, illustrating perivascular infiltration.

B. Systemic Cortisone Therapy.—The effect of systemic cortisone therapy, in reversing an attack, was investigated. This was done by allowing an attack to progress until there was a definite increase in the number of circulating eosinophiles and in the difference between the exophthalmic measurements of the two eyes. The patient was then given cortisone orally in a dose of 300 mg. the first day, 200 mg. the second day, and 100 mg. per day thereafter. Within 24 hours after beginning treatment there was subjective improvement, and within 48 hours there was a decrease in circulating eosinophiles, from approximately 1,000 to 400 or 500 per cubic millimeter, as well as a marked decrease in the difference in the exophthalmic measurements of the two eyes. Within five days after beginning cortisone therapy, the patient was subjectively and objectively normal. A typical response to this therapy is illustrated in Figure 10.

The effectiveness of systemic cortisone in reversing an attack has been demonstrated many times. On one occasion, when the patient was not hospitalized, he was given a three-day supply of cortisone and was instructed to begin therapy as soon as an attack began and to return to

the hospital as soon as possible. The patient stated that within 48 hours after starting the cortisone therapy he was entirely asymptomatic. He was unable to return to the hospital until the fifth day after the onset of the attack and had been without cortisone for 36 hours. His symptoms had recurred, and the difference in exophthalmic measurements was 4 mm. The patient was again placed on 100 mg. of systemic cortisone per day; within 36 hours he was again objectively and subjectively asymptomatic and remained so while receiving cortisone therapy. This therapy was continued for six days and then was withdrawn abruptly. The patient stated that his symptoms returned within 48 hours after discontinuing cortisone therapy. This recurrence was 12 days after the initial onset of this attack and 41 days after the onset of the preceding attack. Five days after the cessation of cortisone therapy, the patient again returned to the hospital, and there was 4 mm. difference in the exophthalmic measurements of the two eyes. The patient was given no further therapy at the time and subsequently stated that this attack progressed and followed through a normal course. Thus, it was not until 25 days after the initial onset of the symptoms that the condition became quiescent. During this interval the symptoms were twice alleviated by systemic cortisone therapy and were finally precipitated after the abrupt cessation of therapy. The relapse that occurred, following the abrupt withdrawal of systemic cortisone, is believed to be due to the effect of adrenocortical suppression.

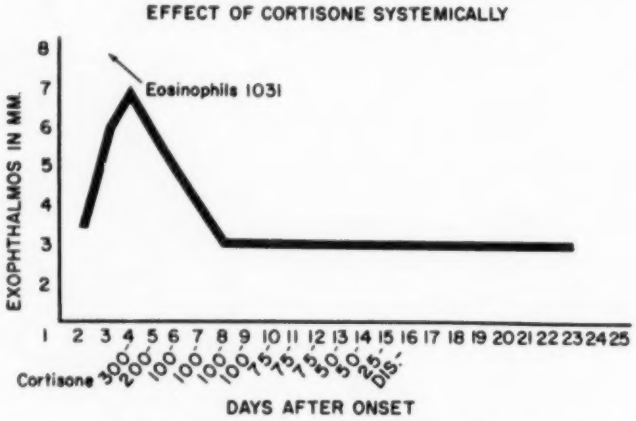

Fig. 10.—Effect of systemic cortisone in reversing an attack of exophthalmos.

C. Diethylstilbestrol Therapy.—The effect of diethylstilbestrol therapy was then investigated. This was done by allowing the patient's acute symptoms to progress for four to five days, until well established, and then reversing them by systemic cortisone therapy, which was gradually withdrawn. After a four-day rest period, systemic diethylstilbestrol therapy was started. It was demonstrated that diethylstilbestrol precipitated attacks and increased the severity of the symptoms. Diethylstilbestrol therapy was given under similar circumstances on three occasions. In the first instance, an attack was precipitated after three days of diethylstilbestrol therapy; in the second, after six days, and in the third, after three days. An average of four days of diethylstilbestrol therapy precipitated an attack. In the first test there was a recurrence of symptoms 22 days after the onset of the preceding attack; in the second, after 23 days, and on the third, after only 18 days. The average time between the diethylstilbestrol-precipitated attack and the preceding naturally occurring episode was 21 days, in contrast to 31 days for naturally occurring attacks. On one occasion, diethylstibestrol therapy was continued for six days after the onset of symptoms, and by the fourth day after the onset the left eye was completely closed and remained so for 48 hours after cessation of diethylstilbestrol therapy.

D. Testosterone Therapy.—Testosterone was given prophylactically, in doses of 5 mg. sublingually five times a day. On this therapy an attack developed and followed through a normal course. Testosterone had no effect on the course of this disease.

E. Diphenhydramine (Benadryl) Therapy.—The effect of diphenhydramine therapy was investigated. The patient was given 50 mg. of diphenhydramine q. i. d. for approximately five days prior to the expected onset of symptoms. On this therapy, an attack developed, and the proptosis of the left eye and the eosinophilia were not affected. Diphenhydramine did not alter the course of the disease.

F. Epinephrine Therapy.—The patient was allowed to develop an attack without therapy. At approximately the peak of the attack the proptosis and conjunctival edema were carefully evaluated. The patient was then given an intravenous drip of epinephrine in dextrose. A good epinephrine response was maintained for one and one-half hours, with no effect on the proptosis or edema.

G. Thyroid Therapy.—The patient was started on dessicated thyroid therapy approximately three weeks prior to the anticipated onset of an attack. The dosage was increased to 5 grains (0.30 gm.) a day, at which level the patient developed mild symptoms of toxicity. In order to demonstrate adequate thyroid depression, the patient was given 50μc of radioactive iodine with only 0.3% uptake in 24 hours, an amount which indicates almost complete suppression of normal thyroid function. This dosage level of thyroid was maintained, and on this program an attack of unilateral exophthalmos developed and followed a normal course. Dessicated thyroid did not alter the course of the disease.

H. Prophylactic Cortisone Therapy.—The prophylactic effect of systemic cortisone therapy was then investigated. The patient was placed on a maintenance dosage of 50 mg. of cortisone a day, and, although the attacks were less severe and no longer incapacitating, they continued to occur at regular intervals on this dosage.

Summary of Case.—A case of rhythmical periodic unilateral exophthalmos with periorbital and conjunctival edema, restricted ocular motility, and diplopia, of three years' duration, is presented. The attacks have recurred at an average of 31-day intervals and have had a mean duration of 14 days. The proptosis was not reducible by digital pressure. Intraocular tensions were normal. The attacks were accompanied by a marked eosinophilia, and the eosinophile count remained elevated during remissions unless reduced by endocrine therapy. There was a tendency to a decreased excretion of 17-ketosteroids. A biopsy specimen of the orbicularis muscle was characterized by perivascular infiltration of eosinophiles and neutrophiles and by connective tissue hyperplasia. An attack could be terminated by systemic administration of cortisone. Diethylstilbestrol precipitated and intensified the symptoms, but testosterone therapy had no effect on the disease process. The syndrome was not affected by diphenhydramine or epinephrine therapy. Prophylactic thyroid therapy did not alter the course of the disease. Prophylactic cortisone therapy modified the severity of the attacks, allowing the patient to continue normal activity, but did not prevent their regular recurrence.

COMMENT

The literature of the last 20 years has been reviewed, and no reports of a similar case have been found. Therefore, there was no precedent to dictate the diagnostic evaluation or mode of treatment in this case. There are many causes of unilateral exophthalmos, but none of these appeared to be applicable to this case. Therefore, the recognized causes of unilateral exophthalmos will not be enumerated or discussed. The most striking feature of this disease process was the rhythmical periodicity with which it recurred. The etiological factors which were suggested were endocrine dysfunction and a local hypersensitive state in the retro-orbital and periorbital tissues. The diagnostic evaluation and clinical investigation have been conducted with this in mind.

The orbicularis biopsy findings and the eosinophilia are compatible with a disease process due to a local hypersensitive state in the retro-orbital and periorbital tissues. Also, the speed of the response to the administration of systemic cortisone is suggestive of an end-organ response, rather than a response through the endocrine system. However, inasmuch as the attacks have occurred when the patient has been removed from his environment and maintained on a controlled diet, and since the course of the attacks has not been altered by antihistaminic chemotherapy or epinephrine therapy, it is believed that an extrinsic allergic factor has been fairly well ruled out. This patient has had numerous examinations for possible parasitic infections, and while End. histolytica has been found, successful treatment of this condition has not altered this patient's disease process. It is extremely difficult to surmise an intrinsic allergic factor which would produce the rhythmical periodicity of this disease process.

Angioneurotic edema has been considered as a possible etiological factor. Unique forms of angioneurotic edema have been reported in the ophthalmologic literature. However, in no report has a rhythmical periodicity been observed, such as was present in this case. It must further be pointed out that the occurrence of eosinophilia is not a part of the disease pattern of angioneurotic edema. Bruun [3] reviewed 46 cases of angioneurotic edema and reached the conclusion that in no case of Quincke's edema alone, i. e., in the absence of other allergic disorders, was any eosinophilia present. He further found that in the majority of cases there was either a past history or a family history of allergy. Callahan [4] reported a case of angioneurotic edema, with attacks affecting either orbit, in which a slight degree of proptosis occurred. Again, eosinophilia was not a part of the picture, and the disease was not rhythmical. Fry and Schlezinger [5] have reported ophthalmoplegia with displacement of the globe due to angioneurotic edema, but, again, eosinophilia was not present nor was the disease rhythmical in its occurrence. Also, in most cases of orbital angioneurotic edema, convulsions or other signs of angioneurotic edema of the brain are present. In both the two cases cited above convulsions were reported. In view of the rhythmical nature of this disease process, the absence of signs of central nervous system involvement, the absence of family and personal histories of allergy and the negative evaluation for allergy, the presence of eosinophilia, and the failure to respond to epinephrine therapy or to diphenhydramine therapy, it is felt that the diagnosis of angioneurotic edema has been ruled out.

The other factor to be considered is endocrine dysfunction. The rhythmical nature of endocrine function and the association of endocrine dysfunction and exophthalmos are well recognized. The basic concept in this regard has been that exophthalmos, due to endocrine dysfunction, is associated with the thyroid-pituitary axis. Mulvany [6] recognized two types of endocrine exophthalmos, namely, the thyrotoxic and the thyrotropic type. Bedrossian [7] believed that both types were due to the production of an excess of thyrotropin, in the first instance with thyroid response and in the latter instance with failure of thyroid response. Rundle and Pochin [8] did necropsies in 17 cases of thyrotoxic exophthalmos and reported that the fat content of the orbital structures was doubled. The relative fat content of the various orbital structures was maintained, but the fat content of each structure was markedly increased. Similar changes were found in other parts of the body, and in cases of thyrotoxicosis without exophthalmos. The authors considered this to be an abnormal

deposition of normal fat. Naffziger and Jones [9] did examinations of the orbital contents in cases of thyrotropic exophthalmos following thyroidectomy and found that the extraocular muscles were three to eight times as large as normal and contained edema and round-cell infiltrations, often in perivascular form. In addition, there was loss of muscle architecture, with increased fibrous tissue and areas of hyalinization. There are certainly many features of these findings that are compatible with the biopsy specimen in this case, illustrated in Figure 10.

Since the advent of adrenocortical and pituitary extracts, much additional research on exophthalmos has been done and results are being published. Many of these observations appear to be conflicting in nature; however, they indicate that the old concept of exophthalmos secondary to dysfunction in the thyroid-pituitary axis will have to be broadened, and perhaps the basic concept modified.

Smelser and Ozanics [10] have used thyroidectomized guinea pigs and produced exophthalmos by the administration of thyrotoxin (Antuitrin T), and subsequently studied the effects of the administration of other hormones on the exophthalmos. They found that estradiol in large doses did reduce the exophthalmos and produced fibrosis of the orbital fat; however, androgens, cortisone, or corticotropin produced no effect. Dobyns [11] has likewise produced exophthalmos in guinea pigs by the administration of thyrotropin and has described histologic changes similar to those described by Rundle and Pochin [8] in thyrotoxic exophthalmos. Dobyns and Rawson [12] and Jeffries * have shown that the thyrotropic factor from the anterior pituitary is distinct from that producing the exophthalmos; however, this factor remains to be identified. Minnow assays for the exophthalmic factor, done by Dr. Brown Dobyns, City Hospital, Cleveland, have been negative in the present case.

The increased incidence of progressive exophthalmos in males as compared with females has been recognized clinically by Radnot,[16] Brain,[17] Dobyns,[2] and others. However, the significance of this role is undetermined. Dayton [18] has reported a fatal case of exophthalmos, with perivascular infiltration of eosinophiles into muscles, and has suggested a possible allergic reaction to sex steroids, as discussed by Phillips [19] and Heckel.[20] Aterman † has reported that the injection of thyrotropin (TSH) into immature guinea pigs produced only moderate exophthalmos, which could be markedly increased by the injection of either cortisone or corticotropin. This intensifying effect was also produced in thyroidectomized animals. He concluded that the intensifying effect of cortisone could not be due to the depression of thyroid activity by cortisone. Aterman also demonstrated that this type of exophthalmos could be reduced by the administration of thyroxin. He concluded that the beneficial effect of thyroxin could not be due to the inihibition of TSH production in the pituitary but may be due to an increased metabolic rate, leading to a more rapid and increased utilization of the excess adrenal steroids.

Hill, Reiss, Forsham and Thorn,[24] and Wolfson and Beierwaltes [25] have studied the interrelationship of the adrenal, pituitary, and thyroid glands and found that cortisone, stress, corticotropin, and epinephrine depress thyroid function; they report a slight temporary improvement in exophthalmos following treatment with corticotropin or cortisone.

* References 13 through 15.

† References 21 through 22.

Aside from orbital decompression, therapy in general has been directed toward altering endocrine function, either through pituitary irradiation ‡ or through the administration of endocrine extracts, e. g., thyroid,[29] cortisone or corticotropin,§ androgen or estrogens,‖ or by combinations of these substances. Varying degrees of success have been reported, from apparent cures to complete failures; and there is no uniformity of results.

The consensus at the present time appears to be that there is a basic principle elaborated by the pituitary which produces exophthalmos. This factor is probably not the thyrotropic factor, but may be closely allied to it. The relation of this aspect of pituitary function to the other endocrine glands and to the gonads is not clear. Whenever one aspect of endocrine function is altered, there is also alteration in production or in function of the remainder of the endocrine system, which may well account for the varying experimental and clinical results reported.

CONCLUSION

A case of rhythmical periodic unilateral exophthalmos is presented. No definite etiological factor has been determined. The therapeutic response in this case, the rhythmical nature of the disease process, and the laboratory data suggest that an endocrine dysfunction either is the etiological basis or at least is associated with the disease. The unique character of this disease process, with the regularity of recurrence and the consistent course of the attacks, makes this case adaptable for clinical study and therapeutic evaluation. Further study is being carried out. This case is published with the hope of stimulating constructive criticism.

ADDENDUM

Since submission of the original paper for publication, it has been found that the attacks of unilateral exophthalmos can be prevented by the administration of 150 mg. of cortisone daily. The patient has been carried on this regimen for 74 days without recurrence, during which he would normally have had two attacks of unilateral exophthalmos.

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ALTERATIONS IN THE FORM, MOVEMENT, AND STRUCTURE OF THE VITREOUS BODY IN APHAKIC EYES

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THE VITREOUS was studied with reference to its movements and attachments in phakic eyes and the results given in a previous paper.[13] The present study includes observations of the form, movement, and structure of the vitreous made on 100 aphakic eyes after intracapsular cataract extraction, in seeking an explanation for certain postoperative complications. Sketches were made of the hyaloid membrane, its ruptures, and the relations of the vitreous to the iris in 67 eyes; the postrotational movements were studied and sketches made in 33 eyes.

CHANGES FOUND

The normal vitreous contains a fossa in its anterior surface, which accommodates the convex posterior surface of the lens. The vitreous hyaloid membrane in this fossa is normally attached to the surface of the lens at Eggers' line. This ring attachment serves to aid in imparting movements of the sclera to the vitreous. The convexity of the lens, too, aids in imparting motion, thus relieving the other vitreous attachments of a portion of the load of the torsional forces causing angular acceleration in the vitreous body. The posterior convexity of the lens also serves to damp the postrotational movements by imparting centripetal acceleration to the rotating vitreous body. When the lens is extracted intracapsularly, anatomic relations in the anterior portion of the eye are altered markedly, with certain mechanical effects. The actions of the lens in imparting rotational forces to the vitreous through its convexity are lost, as are the damping effects during postrotational movement. The attachment at Eggers' line is severed, thus causing increased load on other attachments. Barring abnormal adhesions, such changes would tend to make the postrotational movements freer-flowing and the excursions wider. The patellar fossa, having lost its anterior support, usually everts, like an umbrella turning inside out. The hyaloid membrane, even though it may not rupture during operation, does so subsequently rather frequently. A new oscillatory movement, involving the iris and the most anterior adjacent layers of the vitreous, is introduced (tremulous iris). This is quite independent of the main rotational and postrotational movements.

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HYALOID MEMBRANE

It is just over 100 years since Hannover * postulated a true membrane about and enclosing the vitreous. The existence of such a membrane has been denied in favor of the concept of a mere surface condensation of a gel. The debate still goes on after a century, without any generally accepted conclusion. From the standpoint of a dictionary definition and physical action, there surely is a membrane present, one which can be observed with a slit lamp. It is of importance in relation to postoperative adhesions, abnormal membranes, and other complications. If one studies the anterior vitreous in postoperative cataract patients with a corneal microscope and slit lamp, it will be seen that this hyaloid membrane takes on a multitude of forms, no two of which are exactly alike (Figs. 1 and 2).

The commonest finding is a dome-like form which bulges through the pupil. The dome may be low with a long radius, or it may have a shorter radius with a full hemisphere or more, protruding into the anterior chamber. In some cases the hyaloid membrane stretches and mushrooms over the pupillary margin, causing a herniation which may, in extreme cases, almost fill the anterior chamber. All gradations, from a membrane which lies in a plane just posterior to the pupil, to a hernia which practically fills the anterior chamber, can be observed. It will be readily understood that any marked change in the form of the anterior surface would change the relation of the various parts of the vitreous body. If there is a net-like structure, such as that described by Grignola, the distribution of force during eye movements may be altered throughout the entire structure in such a way as to make definite lines of abnormal tension. Presumably, during the development and growth of the vitreous, the internal structure develops with reference to a pattern of the distribution of forces. When the shape of the vitreous body is markedly altered, the pattern of the distribution of forces must also be markedly altered, causing abnormal strains and stresses in the internal structure and upon the external attachments.

The hyaloid membrane postoperatively is frequently found to be adherent to the iris, with attachments that are so fine as to be practically invisible. In such a case, if the anterior surface is dome-like, the dome is found to be smaller and more spherical when the pupil is contracted and more flattened when the pupil is dilated. It may well be that these normal movements of the attached iris cause the commonly observed late rupture of the hyaloid membrane. In any case, holes and defects in the hyaloid membrane are frequently seen. In some instances of holes, the margins are invisible, and their presence is marked by the protrusion of visible vitreous fibrils into the anterior chamber. In others, the margins of the hole can quite readily be visualized by painstaking use of the slit lamp. Occasionally the vitreous elements protruding through such defects will become adherent to the incision. This may occur long after the period of time ordinarily considered necessary for healing of the incision. It is in these cases that the eye becomes irritated and macular degeneration may follow.[14] This is presumably due to the taking up of slack in the internal structure between the anterior portion of the vitreous and the macular attachment. Under such circumstances, undue stress would fall upon the macular attachment during ordinary ocular movements.

Delicate as the hyaloid membrane is, adhesions to it, perforations through it, and unusual shapes may persist for many years (Fig. 2 *B*).

* References 10 and 11; cited by Duke-Elder.[8]

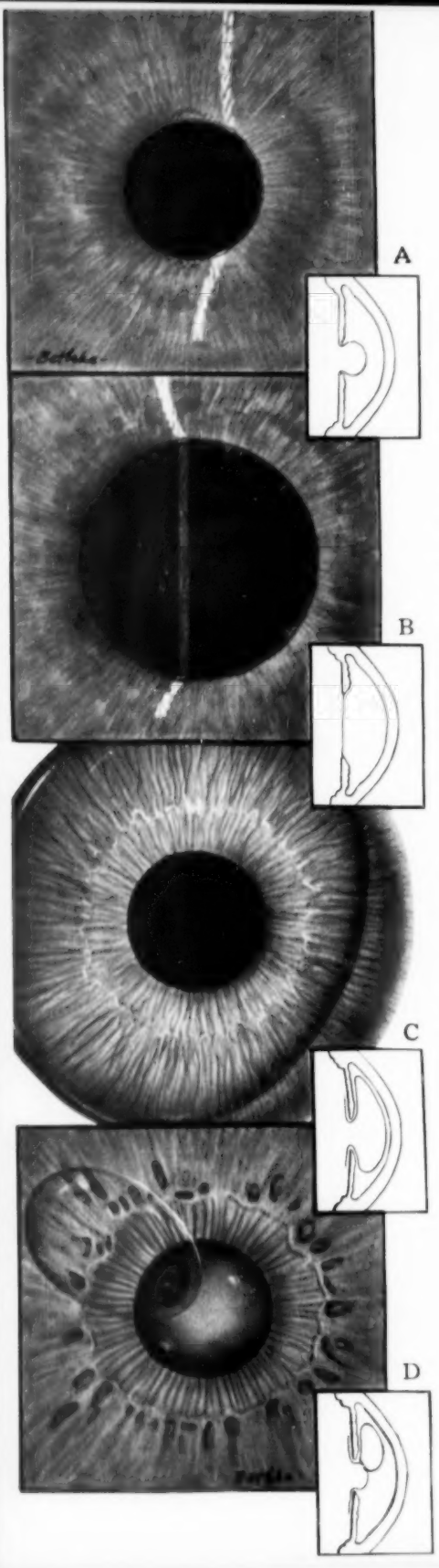

Fig. 1 (left).—Hyaloid membrane after intracapsular lens extraction. The patellar fossa usually everts when it loses the support of the lens. As a result, the hyaloid membrane and anterior vitreous assume a wide variety of forms. The commonest is a simple dome, on the sides of which the pupillary margin slides back and forth, often leaving a little pigment in the zone of contact. Sometimes the pupillary margin is attached to the hyaloid membrane by practically invisible attachments, as in *A* and *B*. In *A* the pupil is contracted, and the hyaloid dome forms two-thirds of a sphere, whereas in *B* it is dilated and the hyaloid membrane is flattened to a plane and is under sufficient tension to show slight gray clouding. It is conceivable that when the pupil is contracted there is traction upon the ciliary body from tension in the hyaloid between the pupillary margin and the vitreous base.

C depicts an unusually large herniation into the anterior chamber, and *D*, a small secondary hernia upon an everted dome. Internal structural relations within the vitreous must be altered by such deformations. There was no demonstrable adverse effect in these three eyes. The postoperative vision in *A* and *D* was 20/20. It was 20/30 in *C* three weeks postoperatively. The patient then went home to a distant state and was not seen again. She reported by letter five months postoperatively that her vision was "good." The vision obtained in the fellow eye was 20/15.

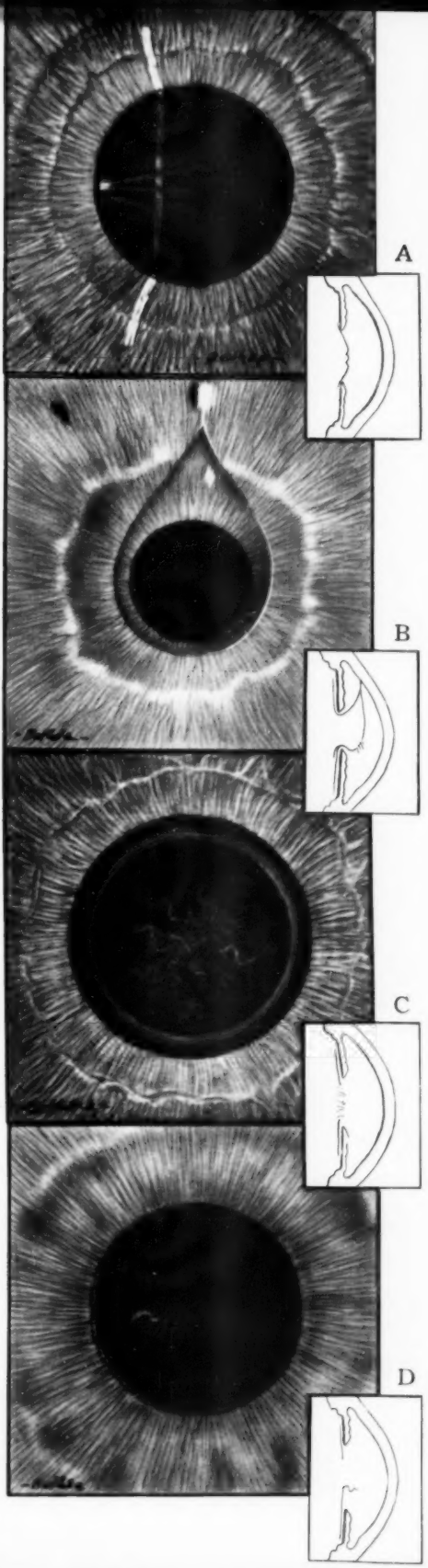

Fig. 2 (right).—Hyaloid membrane intracapsular lens extraction.

A, a small adhesion at 6 o'clock which made tension in the hyaloid membrane when the pupil was dilated, but was invisible and made no tension when the pupil was contracted and the protruding dome of the everted hyaloid formed a larger part of a smaller sphere. Vision was 20/20. This eye was tested for postrotational movement. The first phase was fast and directed upward in the deeper portion of the vitreous. The more anterior part was tied to this adhesion and could not follow. It was snubbed short with traction upon the adhesion. The traction during rotation must have been even greater than in postrotational movement. If such an adhesion had existed at the retina, the latter might very well have torn. The mechanism of tear could be readily observed in this eye.

B, small hernia adherent by a thin strand of adhesion tissue to the operative incision at 12 o'clock. There was a small hole through the hyaloid membrane in the lower part of the hernia through which vitreous strands protruded. This appearance of the hyaloid was first noted 12 years postoperatively and was unchanged 14 years after operation. Vision 20/30.

C, a central hole through the hyaloid, almost as large as the dilated pupil, two and one-half years postoperatively. The vitreous substance surged back and forth through this hole during eye movements and during accommodation but was not adherent to either cornea or iris. Vision 20/20. When such protruding vitreous becomes adherent to the line of incision, it may cause anteroposterior tension through the vitreous body, with serious damage to the macula.

D, unusual tear with an operculum, as seen two years postoperatively. It is not known when this tear occurred, but it was probably at the time of operation. Vision 20/20.

TECHNIQUE FOR STUDY

The technique for study of postrotational movements was very simple. Observations were made through the corneal microscope. The patient was asked to fix at some point on the microscope and then, after having turned the eye 30 degrees one way or the other, to return quickly to this point of fixation. The vitreous movements during actual rotation cannot be observed in this way, but the slower postrotational movements, which continue after the eye has come to rest, can be readily seen and studied. From these postrotational movements one can deduce possible mechanisms for intraocular trauma, such as retinal tear and macular damage.

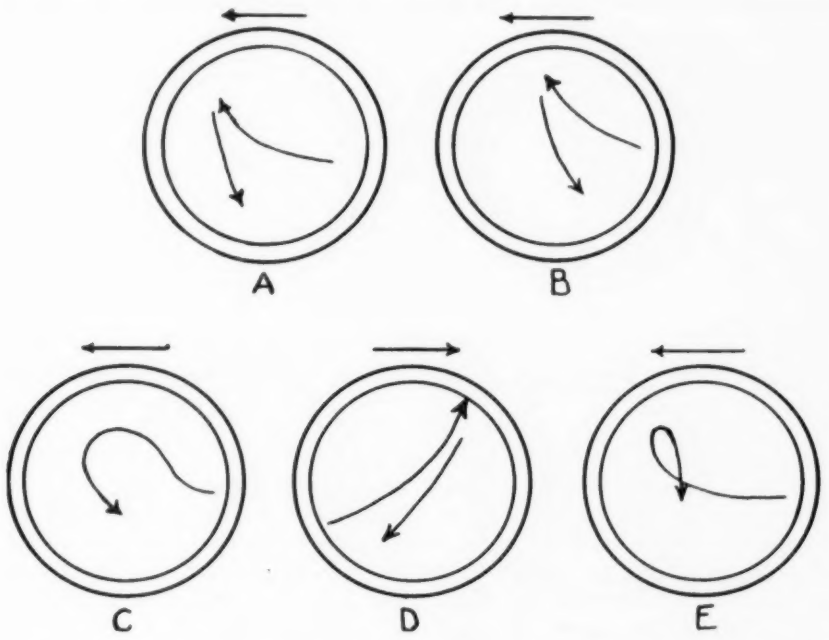

Fig. 3.—A, diagram of postrotational movement (p.r.m.) two years postoperatively. The p.r.m. was normal, even though the hyaloid membrane was adherent to the iris. Vision 20/20+.

B, normal p.r.m. two and one-half years postoperatively. Vision 20/15.

C, pattern of p.r.m. 11 years postoperatively. The vitreous seemed looser than normal, with a wide, sweeping, slow first phase, which blended directly into the second phase to make a spiral. Vision 20/15.

D, the p.r.m. 10 years postoperatively. It was freer-flowing and more sweeping than usual, but was otherwise normal. The hyaloid membrane in this eye was tight and gave back polychromatic reflections. Vision 20/30+.

E, a free-flowing, wide spiral as described in the p.r.m. of this eye three years postoperatively. There was a central hole in the hyaloid membrane but no vitreous adhesions. Vision 20/15—.

POSTROTATIONAL MOVEMENTS IN APHAKIC EYES

Normal.—The postrotational movements are found to be within normal limits in some aphakic eyes. It may be that even in these eyes there is some change as compared with the preoperative movement, but, so far as one can tell by looking at

them, they are within the range of normal. Two cases in point are illustrated in Figure 3 *A* and *B*. In both these cases the hyaloid membrane was intact and no abnormal adhesions were observed behind it.

Increased Fluidity.—It would be expected that with the loss of support of Eggers' line and the loss of the effect of the posterior surface of the lens, the rotational and postrotational movements would be freer-flowing and have wider excursions than normal. This actually does occur, as found in three cases illustrated in Figure 3 *C*, *D*, and *E*. In these eyes, also, there seemed to be no adhesions behind the hyaloid membrane, although two showed a central hole. When observing the postrotational movements in such eyes as these, one receives the impression that the vitreous is much more fluid than normal. That may not be the case; the impression may simply

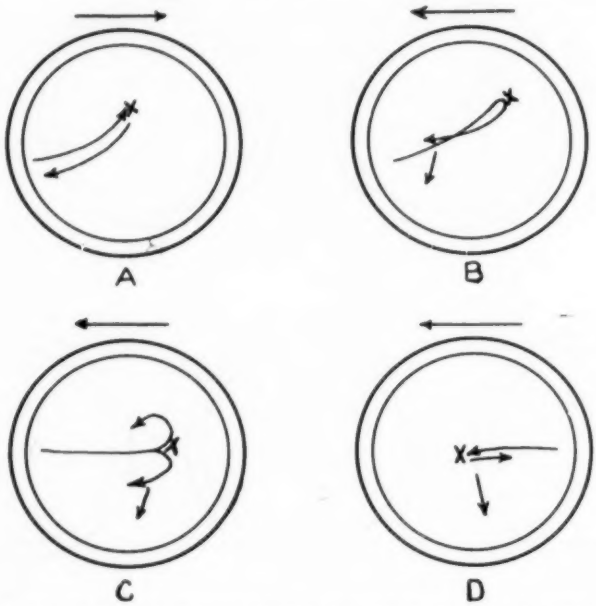

Fig. 4.—All four of the eyes illustrated in this figure indicated some invisible obstruction in the vitreous at the points marked *X*, resulting in definitely abnormal p.r.m. but with no effect on vision or other complications.

A, 14 months postoperatively. The first phase rebounded sharply at *X* directly into a fast second phase, which practically duplicated the line of flow of the first phase. The hyaloid membrane contained a number of holes and presented a moth-eaten appearance. Vision 20/20.

B, two and a half years postoperatively. The first phase was fast and at *X* spiraled back with a bounce in the reverse direction. The second phase flowed normally. The hyaloid membrane could not be identified with certainty. There were two membranes: a taut anterior one, which covered only half the pupil and had a rolled edge, and a thinner one, lying slightly posterior, containing a central hole. Vision 20/15.

C, seven years postoperatively. The first phase split beyond the center at *X* to make two spirals, as indicated. The second phase was about the usual normal one. Vision 20/20.

D, 11 years postoperatively. The first phase was short and fast, with a sharp rebound. The second phase was short and rather slow. Vision 20/20.

be due to wider excursion on account of loss of attachments, support, and damping. The fact that the vitreous is freer-flowing than usual does not necessarily indicate a dangerous or an undesirable condition.

Rebounds and Snubbing.—The postrotational movements in other eyes indicate quite clearly that there are abnormal adhesions, or at least lines of tension in the vitreous, which could cause complications. These lines of tension or adhesions, if such they are, are marked by peculiar rebounds, eddies, and spirals in the vitreous movements and an appearance suggesting that the vitreous is snubbed short and stopped with a jerk or is sharply deflected. The direction of flow may be altered, as may the amount of excursion. In Case 11 the movements in the right eye were normal. In the left eye the hyaloid membrane was full of small holes, giving a moth-eaten appearance. In left rotation the first phase of postrotational movement was up and out with rebound into the second phase, which followed the same course in reverse, as though the moving vitreous had struck a taut rubber band and bounced back (Fig. 4*A*.) In Case 5 the first phase was in the direction of rotation, somewhat upward and very rapid. At a little distance to the left of the center, it seemed to strike an obstruction which deflected it downward and in the reverse direction, to describe a fast spiral. This entire spiral seemed to be in the first phase. When this spiral movement ceased, the second phase of settling began (Fig. 4*B*). Still another form of flow was found in Case 12. In this left eye, the streaming first phase appeared to strike an obstruction in the lateral part of the eye, at which the flow divided, describing two spirals, one of which turned upward and the other downward (Fig. 4 *C*). In Case 10, in the right eye was found a short, sharp rebound in the first phase, almost in the center of the eye, which was followed by the slow second phase with settling (Fig. 4 *D*). The first phase in the left eye (also aphakic) was much more flowing and was directed first laterally and then almost straight up, to rebound as though an obstruction had been encountered in the upper part of the eye.

VISIBLE ADHESIONS

Definite adhesions of the vitreous were found in a number of cases, some of which did not seem to be doing any particular harm. In Case 16 the hyaloid membrane was ruptured and there was an adhesion of the vitreous to the corneal incision. The iris was notched where the vitreous strands crossed the margin, and the postrotational movements showed rebound characteristic of snubbing. There seemed to be no effect, however, upon the vision, which was 20/20. Another type of adhesion is that found in Case 15, left eye, in which a mass of vitreous was adherent to the posterior surface of the hyaloid, and through this to a posterior synechia at 6 o'clock. The movements of the vitreous mass during rotation and the character of the pull on the adhesions could be very well observed. One could readily understand how adhesions of this nature, if they attach the vitreous to the retina, might tear the latter.

Adhesions with Macular Damage.—Not all the vitreous adhesions found were harmless. In Case 2 a horsetail adhesion to the corneal incision developed. The patient had normal vision (20/20) in the immediate postoperative period, but, in the months which followed, the eye became irritated and she lost central vision, the syndrome described so well by Irvine.[14] This patient's vision was reduced from an initial 20/20 to 20/50 during the first few postoperative months, and her visual field contained a relative central scotoma. The vision, however, returned to 20/20 by the end of the year, at which time no definite macular pathology could be seen. Another such patient (Case 13; Fig. 5) followed a similar course. The hyaloid membrane ruptured, and there developed a vitreous adhesion to the line of incision between

10 and 11 o'clock. His vision at the end of six weeks was 20/20. Then, during the next four or five months, he had recurrent attacks of irritation and pain, and the visual acuity fell to 20/100. The macula showed definite signs of pathology, and he had a relative central scotoma. Fortunately, in this patient, too, the damage at the macula seemed not to be permanent, at least from the standpoint of function. At the end of 10½ months the eye was quiet and vision had returned to 20/30+, despite

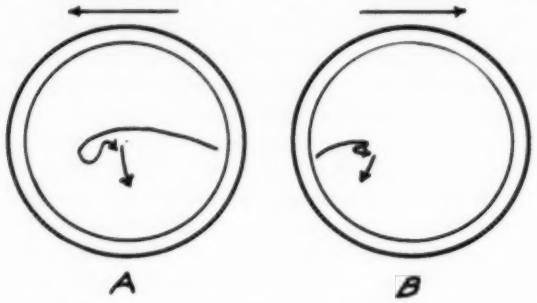

Fig. 5.—Ten and one-half months postoperatively. The hyaloid membrane in the right eye was ruptured and a horsetail vitreous adhesion developed at 11 o'clock, with notching of the pupil. Vision at the end of six weeks was 20/20, and at the end of six months, 20/100. Fundus examination revealed macular pathology. The eye eventually quieted down, and visual acuity returned to 20/30+, even though the macular lesion remained visible. (*A*) After right rotation p.r.m. was rather free flowing, with a downward spiral behind the 11 o'clock incision, as indicated. In left rotation (*B*) the first phase was stopped sharply short of the center, where a one and a half cycle oscillation took place. This point of obstruction lay behind and somewhat inferior to the horsetail adhesion. It is likely that this invisible obstruction represented an anteroposterior shortening of the vitreous structure between the corneal adhesion and the macula with a line of tension present here, at least during motion of the vitreous.

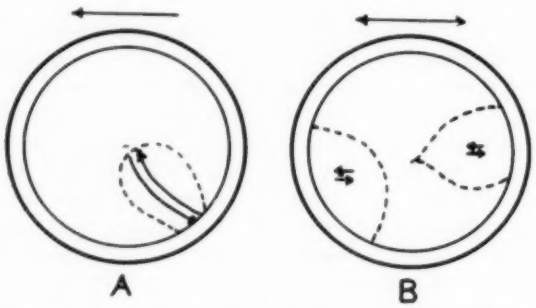

Fig. 6.—*A*, three and a half months postoperatively. The 86-year-old patient had central retinal atrophy and arteriosclerotic degeneration with a hemorrhage. The retina could not be visualized preoperatively. Vision limited to hand movements.

The vitreous was largely liquid but contained a blob of formed vitreous attached somewhere in the lower nasal quadrant. In p.r.m. it floated sluggishly up into view, as indicated, and then sluggishly settled back again. It is unlikely that it made any considerable traction. The hyaloid membrane was slack and torn on the nasal side. It was tremulous, like the iris, and waves could be observed passing over or through it.

B, seven months postoperatively. In this (left) eye there were two blobs of formed vitreous, one on each side, with an optically empty zone between them. Both seemed to be attached in the region of the ciliary body, and the temporal one was also adherent approximately in the center of the pupil to taut horizontal strands in the hyaloid. The hyaloid was ruptured above these strands. Both exhibited very brief and limited p.r.m. In each, the first phase was short and fast, with a sharp rebound. There was practically no second phase. In other words, both these masses were closely attached to the wall and rotated and stopped almost with the sclera and cornea. Vision 20/30.

the fact that the changes at the macula remained clearly visible. The vitreous adhesion, of course, remained unchanged. It may be that in both these patients the normal vitreous attachment at the macula eventually gave way, thus relieving the macula of abnormal traction. Vitreous detachment at this point is not unusual either in phakic or in aphakic eyes.

Adhesion with Detachment.—One patient (Case 4) developed an adhesion of the vitreous to the incision, which was followed by detachment of the retina. The tear was found and repaired, with good mechanical result. The macula, however, had been detached, and central vision remained poor for some months but, after nine months, improved again to 20/40+.

Detachment occurred also in a young boy (Case 9), who had been operated upon for congenital cataract two years earlier. A pupillary membrane developed, which was removed in a two-stage operation. In the first stage, an incision was made two-thirds or three-fourths of the way around the circumference of the pupil and the pupillary membrane cut into a round flap, which remained attached at one side. At a subsquent operation, this flap was grasped and cut with a small scissors, which was entered into the eye. The vitreous was invaded by the knife at the first operation and by the scissors at the second operation. Detachment followed some time later, and attempts to repair it failed.

SHRUNKEN VITREOUS

Occasionally masses or blobs of vitreous, such as those described by Pischel,[17] may be seen. In Case 6 a large mass of vitreous attached in the lower outer quadrant floated up into view with every movement of the eye and then settled down again, to disappear into the bottom of the eye. The movements seemed to be quite free, and, as far as could be determined, the mass was doing no harm (Fig. 6). Another instance was that of Case 8. In this eye there had been three peripheral iridectomies. The one at 12 o'clock was purposely extended through the sphincter of the pupil, and one of the others tore through the sphincter, accidentally leaving an L-shaped pupil. The vitreous was adherent at 12 o'clock. There were tight strands in the anterior vitreous face across the lower half of the pupil, in the center of which there were attachments to the vitreous lying behind. Two large blobs of vitreous were seen, which were not attached to one another; one was attached medially and below and the other laterally, presumably at the vitreous base in both instances. Between the two there was an optically empty space. The medial blob seemed to be intimately attached to the wall of the eye and moved almost with it, having a very short postrotational movement and a sharp rebound. Deep in the vitreous on the medial side, posterior to this blob, there was a small circular postrotational movement. The lateral blob seemed to be suspended between the center of the strand spanning the pupil and the vitreous base laterally. In this mass, also, the movements followed those of the sclera very closely. There was an exceedingly short postrotational movement with a sharp rebound. As yet, no harm has been done in this eye by these abnormal conditions. The vision is excellent (20/20—4), but obviously the vitreous structure and its rotational and postrotational movements and the forces involved have been very radically altered.

LIQUEFIED VITREOUS

Case 3 is that of a one-eyed clergyman (the other eye having been lost after cataract extraction abroad) in whose only eye cataract developed. Before operation he was highly myopic, wearing a —20.00 sph. ⊂ —2.00 cyl., ax 105. He had had a previous optical iridectomy. We did our usual intracapsular operation, without any complications. The vitreous was studied five years postoperatively. The hyaloid membrane was found to be ragged. In the vitreous, which seemed to be almost entirely liquid, many visible fibrils floated about as the eye moved. As soon as the eye came to rest, they quickly settled to the bottom. These fibrils seemed to be attached at the periphery and, as the eye rotated in either direction, would snap up into view and assume a more or less horizontal position, like a ragged flag waving in the wind. The postrotational movement was so brief in either direction that it was difficult to catch. The fibrils seemed to be attached—some medially and some laterally—at or behind the ciliary body, but they did not seem to be any part of formed vitreous. The fibrils were separated in the middle, leaving an optically empty space. In this eye, there seemed to be little or no formed vitreous. The fibrils appeared to be almost without mass and to be floating free in a liquid almost like water. It would seem that an eye like this would not be in any danger from retinal detachment of the vitreous type because there is no formed mass of vitreous sufficiently large to cause any considerable pull upon the attachments. The vision is good for an eye with such high myopia (20/40—1). He wears now as a cataract lens +0.50 sph. ⊂ —3.75 cyl., ax 85; add +2.50 sph.

COMMENT

The possibility of damage to the vitreous through cataract extraction should be given serious consideration. Under the best of circumstances, the shape of the vitreous is altered. The anteroposterior dimensions are increased, and it is quite probable that definite changes in the internal structure occur whenever the lens is removed. Manipulation and distortion of the vitreous during operation seem likely to increase damage to the internal structure. As far as the vitreous is concerned, intracapsular cataract extraction causes a lengthening similar to that occurring in myopia. Just as retinal detachment occurs more frequently in myopes than in emmetropes or hyperopes, so the incidence of retinal detachment is greater in aphakic eyes than in phakic ones; and the tear is more difficult to repair. It is very likely that the increased incidence of detachment is related to derangements of internal structure or external attachments of the vitreous, together with alteration in the distribution of rotational forces. The incidence of retinal detachment following surgical treatment of congenital cataract or the discission operation is much greater than that following intracapsular lens extraction.† It is obvious that the vitreous cannot be invaded with impunity.

The hyaloid membrane frequently becomes attached to the iris after intracapsular extraction. How this attachment is related to Eggers' line, I do not know. In any case, when it is so attached to the iris, the everted patellar fossa changes shape every

† The incidence of retinal detachment is much higher in aphakic than in phakic eyes. Duke-Elder,[8] citing Arruga, gives it as 2% after intracapsular operation. After discission it is much higher than that. Shapland, also cited by Duke-Elder, gives a figure of 10.7%. Some surgeons have had detachments in as many as 20%. In my own series, the incidence has not been as high as these figures after either operation.

time that the pupil changes size; and when the pupil is dilated, the hyaloid membrane is sometimes stretched to the point where it becomes grayish. Often the hyaloid membrane subsequently ruptures. Sometimes vitreous fibrils protrude through the rupture and become adherent to the cornea. These adhesions may or may not cause complications. They are sometimes followed by macular damage, presumably from tension transmitted through the internal vitreous structure.

The cycle of rotation incident to all normal ocular movements includes angular acceleration, peak velocity, deceleration, and rest. The period of time required for this cycle is much greater in the vitreous than in the sclera. This increased time decreases the force necessary to rotate the vitreous,[13] thus protecting the attachments of the latter from undue strain. In some of the aphakic eyes examined, it was found that large portions of the vitreous were moving almost in unison with the sclera. In other words, the protective slack and lag had been lost through shortening of the internal structure, or through abnormal adhesions, or in some other way. Such increased acceleration in velocity in the vitreous must, from the standpoint of physics, increase the force of the pull on the vitreous attachments to an abnormal degree,

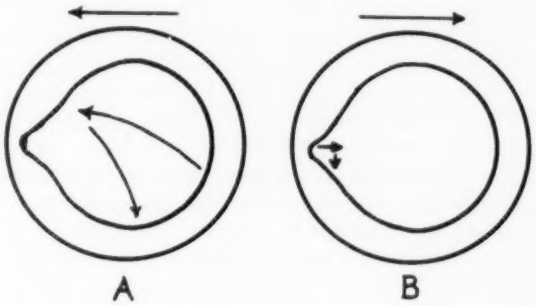

Fig. 7.—*A*, right eye eight and a half years postoperatively. There was an adhesion at 9 o'clock involving the iris, hyaloid, and anterior vitreous structure. A series of tight bands in the hyaloid fanned out across the pupil from the point of adhesion, between which the hyaloid was open. The vitreous did not seem to be adherent to these bands. In fact, it gave the appearance of being more or less liquid. In right rotation (*A*) the p.r.m. was sweeping and free flowing, but in left rotation (*B*) both phases were snubbed short at the adhesion, as indicated. Vision 20/30.

unless the formed mass of vitreous is correspondingly reduced. It seems quite likely that this loss of slack and lag in the vitreous, with the resulting increase in the force necessary to produce angular acceleration, may account for some retinal tears. On the other hand, if the mass of formed vitreous is reduced, as in Case 6 (Fig. 6), the pull at the attachments may not be increased to the danger point. When the vitreous becomes more liquefied, as in Case 3, that of the clergyman, it is quite conceivable that the force of the pull may be decreased because of the smallness of the remaining amount of formed vitreous to be rotated. Another eye has subsequently been observed, in which vitreous fibrils had become adherent to the corneal incision line and subsequently had lost their connection with the remainder of the vitreous. They dangled harmlessly, like loose threads.

In Case 17 (Fig. 7), and in some of the other cases cited above, there seemed to be more or less taut bands spanning a portion of vitreous, which acted to obstruct the postrotational movements. One can only conjecture as to what effect they might

have. It is quite obvious, in any case, that when the vitreous has been disturbed by cataract extraction or when it has been invaded by instruments, the incidence of retinal tear from normal ocular movements is very greatly increased. When the lens is extracted intracapsularly, the zonular fibers are released and the support of the lens and its frame are lost. In addition, there is undoubtedly damage to the ciliary body, as evidenced by postoperative hypotony. There may be postoperative tugging upon the ciliary body from a taut hyaloid membrane when an adherent pupil is contracted. A certain amount of fibrosis about the ciliary body and zonule is not unlikely; this may have some effect upon the increased incidence of retinal disinsertion at the ora.‡ I believe that ophthalmic surgeons should become increasingly aware of the possibility of dangerous damage to the vitreous during intraocular surgery, even though no vitreous is lost and though the hyaloid membrane may be intact at the end of operation.

SUMMARY

The internal vitreous structure may be more or less altered in so-called uncomplicated intracapsular cataract extraction. This is evidenced by alterations in the postrotational movements seen in the vitreous. The change may be an increase in anteroposterior dimension, or it may be a rupture of the hyaloid membrane with adhesions to the iris or cornea; lines or zones of tension; detachment and shrinkage of the vitreous, separation of the vitreous into divided masses, and more or less complete liquefaction. The angular acceleration and the velocity may be increased. The duration of postrotational movement may be increased or decreased, as may the amplitude of the excursions. Complications at the time of operation enhance these changes and seem to be greater when the vitreous is actually invaded by instruments, as in discission and needling operations.

That changes in the vitreous are important is evidenced by the intraocular adhesions, postoperative irritation, macular changes, and increased incidence of retinal detachment. Apparently, most retinal detachments are not caused by the major vitreous attachments—those at the disc, macula, lens, and base on the vitreous body. Rather, they seem to be caused by minor or abnormal attachments between the retina and the vitreous body at or anterior to the equator.

‡ Even though extracapsular extraction avoids some of these difficulties, it causes worse and numerically greater complications in the form of iritis and secondary pupillary membrane, which must be needled.

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MECHANISM OF SACCADIC EYE MOVEMENTS

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DODGE, who was the first systematically to study and classify the various types of eye movements, attached the name "saccadic movement" to the rapid changes in position of the eyeball which are typically found between fixational pauses during reading. He also observed that the movements constituting the fast phase of optico-kinetic and vestibular nystagmus have similar characteristics. Most experimenters have found that all voluntary movements executed in the absence of a moving visual stimulus are saccadic, and even "pursuit" movement patterns, in response to moving visual stimuli, can be demonstrated to contain saccadic components. This widespread occurrence of saccadic movements in the normal human and the fact that they can be observed in very young infants and in lower species with good ocular motility suggest that they constitute a basic response pattern in the oculomotor system.

The mechanism by which the changes in eye position characteristic of saccadic movements are produced is by no means clear.

One prerequisite to a full understanding of the physiological mechanisms of saccadic movements is a series of accurate records of the changes in eye positions during these movements. The present paper describes an experimental procedure which appears to satisfy most objections that may be leveled at previous attempts to obtain such records.

The most reliable method for recording eye movements is probably the one developed by Dodge, in which rays from a light source reflected by the cornea (corneal reflex) are brought to a focus in the plane of a moving photographic plate or film. Dodge's results,* while classic, cannot be used as more than a guide to the changes in eye position during movements, because he neglected to secure accurate calibration of the eye-position dimension of his recording system.

Another experimenter who has contributed greatly to this field is C. H. Judd. Judd's data † are valuable because he was able to record horizontal and vertical movements of the eyes simultaneously, but he lost resolving power in the time dimension in this way and his studies are, therefore, not too reliable as guides to the temporal sequence of events during eye movements.

Considerable attention has been given to the study of eye movements during reading, but the techniques employed for this purpose †—designed to measure the number of fixations per line of print and suchlike—do not yield records sufficiently

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* References 1 through 3.

† References 5 and 6.

accurate for the analysis of the nervous and muscular mechanisms subserving an eye movement. This applies particularly to the electrical method.[7]

The various techniques developed for the study of the small movements during steady fixation, insofar as they differ from the above, either do not lend themselves to the recording of more extensive movements or have not been applied in this direction.

The contact lens method of Ratliff and Riggs [8] and of Ditchburn and Ginsborg,[9] which would be particularly applicable, since it insures that the records are not contaminated by translational movements, cannot be used for accurate recordings of larger eye movements, because a contact lens does not follow the eye precisely in its larger excursions.

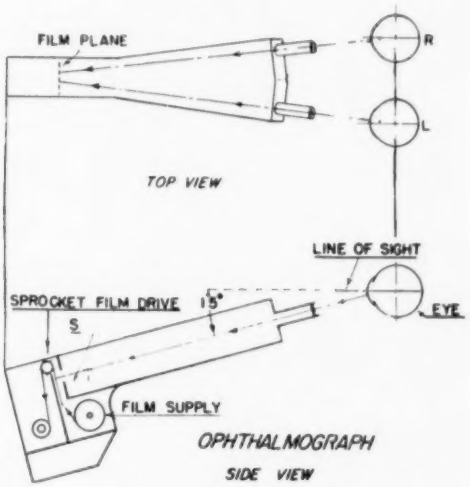

Fig. 1.—Diagram of eye movement camera used in the experiments.

APPARATUS

The method which provided the data upon which the present study is based appears optimal for the purpose. It has been possible, where needed, to secure continuous photographic records of the horizontal movement of both eyes. The resolving power in the time dimension is about 1 msec., and the position of the eye is registered with a precision of 5 to 10 minutes of arc.

The apparatus (Fig. 1) consists of an American Optical Company Ophthalmograph eye movement camera, on which the following modifications were made:

1. The film was moved by a sprocket wheel driven by an assembly designed to keep the motion at a uniform rate and free from chatter. The assembly was driven by an electric motor geared down by a series of pulleys to keep the film moving at the desired speed.

2. A narrow (less than 0.1 mm.) horizontal slit was positioned in front of the film.

3. The lenses in the camera were replaced by a pair of coated achromatic lenses of 26 mm. aperture and 90 mm. focal length, which were combined with a pair of 1.50 D. cylindrical lenses oriented so that a point object was imaged as a vertical streak in the plane of the film.

4. The illuminating system consisted of a pair of streak filament bulbs. The images of the streaks, oriented vertically, were focused a little behind the centers of curvature of the corneas.

The combined effect of modifications 3 and 4 is to produce in the plane of the film a vertical-streak image of the corneal reflex. A narrow part of this vertical streak is intercepted by the horizontal slit, thus isolating purely the horizontal component of the movement of the streak across the slit.

During most parts of the experimentation the film speed was 87 mm. per second. The resolution and steadiness in the time direction are illustrated in the upper portion of Figure 2, which shows a section of film that was intermittently illuminated by a Strobotac flashing 250 times per second.

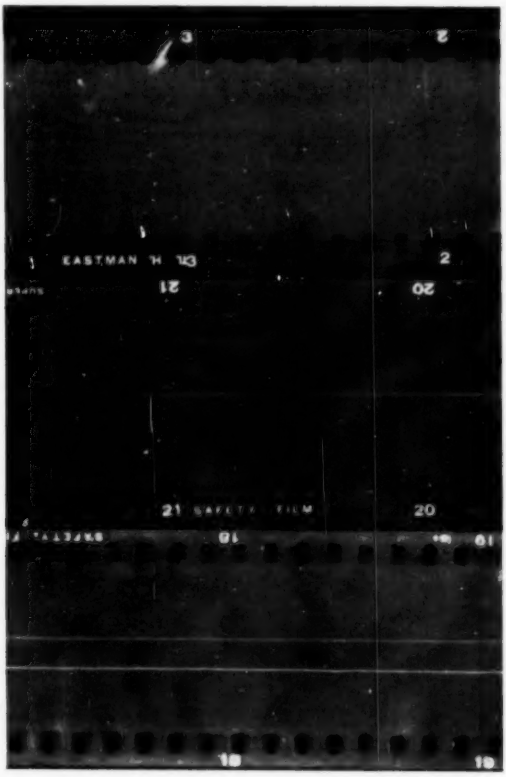

Fig. 2.—Performance of the camera after modification.

Upper, record when slit was illuminated by a Strobotac flashing at the rate of 250 per second.

Middle, record with contact lens clamped to subject's bite bar.

Lower, trace of corneal reflections from both eyes during "steady" fixation. Separation of the traces of the two eyes corresponds to an eye movement of about 11 degrees.

In order to test for steadiness in the direction of eye movements, a contact lens was clamped to the subject's bite bar and a record obtained in the ordinary manner. A section of it is shown in Figure 2, middle portion.

Figure 2, lower portion, shows the trace of both corneal images of a subject during binocular steady fixation of a light spot 10 minutes of arc in diameter situated in the median line 150 cm. in front of the observer. It will be seen that the width of the trace is equivalent to an eye movement of about ¼ degree and that variations in position of the trace of about a half its own width are clearly discernible and possibly capable of measurement. It is

estimated from this record that the resolving power in the lateral direction, i. e., at right angles to the time direction, of the apparatus as used is of the order of 5 minutes of arc; i. e., changes in eye position of about 5 minutes can be recognized on the record. The subject's head is held firmly in position by a bite board with a wax impression of the subject's teeth.

Comparison of the middle and lower portions of Figure 2 shows the unsteadiness of the trace during "steady" fixation. This may correspond to the eye movements during steady fixation, which have been so abundantly demonstrated (Adler and Fliegelman,[10] Lord and Wright,[11] Ratliff and Riggs,[8] Ditchburn and Ginsborg,[9] Barlow [12]). Not very much attention is being placed here on this point, however, since these phenomena are about at the threshold of the resolving power of the apparatus and since one cannot be certain that lateral or rotational head movements of this order are being completely eliminated by the use merely of a bite bar with a wax impression of the subject's teeth.

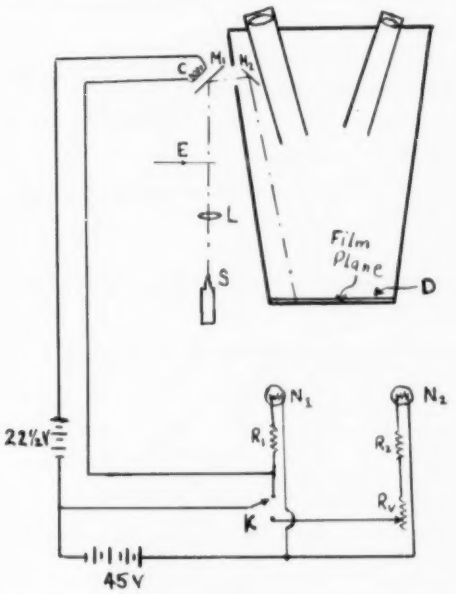

Fig. 3.—Apparatus for presenting stimuli for saccadic eye movements.

The correlation between extent of lateral excursion (rotation) of the eyeball and the distance through which the trace moved laterally across the film was established experimentally for each subject. It was found that over a median 25 degrees, i. e., 12½ degrees on either side of the primary position, this relation is linear, but that it falls off sharply from linearity as the extent of the movement increases. Care was taken for the purpose of analysis to use only those parts of the trace falling within this linear range.

PROCEDURE

Two neon bulbs (N_1 and N_2) were mounted so that they could be moved to any position on a horizontal arc of 150 cm. radius centered on the midpoint of the base line connecting the centers of rotation of the subject's eyes. They were connected by an electric circuit (Fig. 3) in such a manner that when the microswitch (K) was pressed, Bulb N_1 would light up and Bulb N_2 would be extinguished, and that the reverse would occur on releasing the microswitch. A light source (S) was positioned so that the lens (L) and the two mirrors (M_1 and M_2) would image it on the film plane a little to the side of the trace of the corneal reflex and, like the latter, be intercepted by D, the diaphragm with the narrow slit.

Mirror M_1 was attached to an electromagnet, which instantaneously (i. e., within about 1 or 2 msec.) assumed different positions on pressing and releasing of the microswitch, and in this way the signal line was displaced synchronously with the change-over from one bulb to the other. The bulbs, incidentally, also lit up and became extinguished instantaneously.

An episcotister disc driven by a synchronous motor was placed at E, intercepting the light rays constituting the signal line every 1/100 second, and in this manner a time scale was established on the record itself.

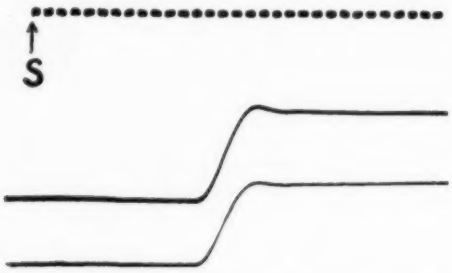

Fig. 4.—Typical record of a 20-degree saccadic eye movement. Stimulus presented at S. Time line interrupted every 10 msec.

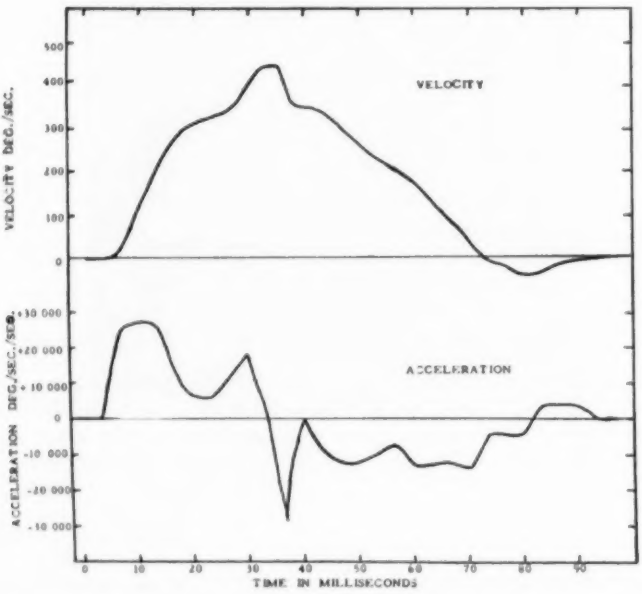

Fig. 5.—Velocity and acceleration changes during a typical 20-degree saccadic movement.

After the calibration record was secured for each subject, the response of the eye to a step stimulus was obtained in the following manner: The subject was instructed to fixate the neon bulb which was lit up, and which was the only target visible in the otherwise dark room, and was told to change fixation to the other target immediately it became visible. Both neon lights

presented a narrow rectangular filament to the subject, measuring approximately 2 mm. in the horizontal direction and approximately 8 mm. in the vertical direction. They had a pinkish glow when current was passed through them, and their luminance was matched by adjusting the variable resistance (R_v).

RESULTS

Responses were obtained for symmetrical positioning of the two targets on either side of the median plane and for angular separations at the nodal point of the eye of 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 25 and 30 degrees. A typical response to a 20-degree step stimulus is shown in Figure 4.

The response exhibits certain characteristics, some of which have not so far been described.

There is a reaction time which varies between 120 and 180 msec. The smaller of these values is somewhat less than previously reported. An analysis of the relation between the extent of the separation of the two bulbs and the reaction time has not

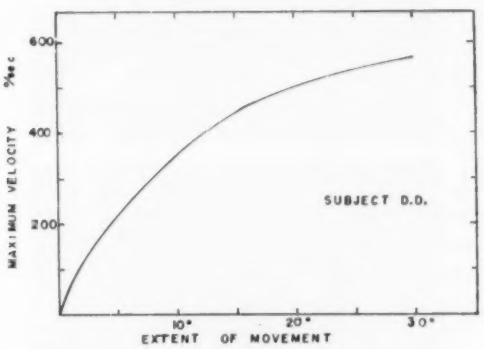

Fig. 6.—Relation between maximum velocity and extent of saccadic eye movements.

been attempted. It would require a randomization of the presentation of the stimuli which was not carried out during the experimentation.

Some of the other features to be noted in Figure 4 are as follows:

(*a*) The high degree of simultaneity of onset of the movement in the two eyes.

(*b*) The rapid acceleration to a velocity that is maintained over a large part of the movement.

(*c*) The overshoot and small oscillations around the final position. This overshoot is to be distinguished from the overshoot described by previous writers. If the first fixation was beyond the correct point and after another reaction time a further movement was made to a more accurate position, this was often referred to as an overshoot of fixation.

Figure 5 shows the change in velocity and acceleration of the eye during the course of a typical saccadic eye movement of 20 degrees. In this connection it is of interest to note that the maximum acceleration of the eyeball showed no significant differences for saccadic movements ranging from 15 to 50 degrees.

In Figure 6 the maximum velocity during a saccadic movement has been plotted against the extent of the movement. It will be seen that the maximum velocity increases as the extent of the movement increases, but that the relation falls off sharply from linearity for more extensive movements.

COMMENT

The records of eye movement responses to visual stimuli show the combined effects of all factors contributing to these movements. With some degree of arbitrariness, we may classify these under two broad headings: first, all factors initiating and contributing to the change in tension of the eye muscles and, second, the mechanical

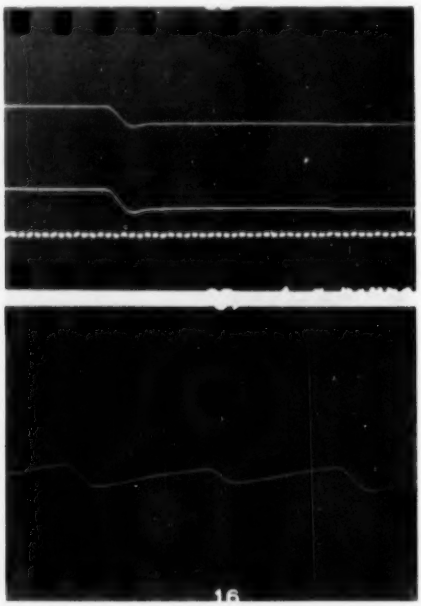

Fig. 7.—Upper record: Normal 6-degree saccadic eye movements. Time line interrupted every 10 msec.

Lower record: Eye movements in a case of congenital "jerk" nystagmus, with subject looking straight ahead. Film speed same as in the upper record.

factors of inertia, friction, and elasticity of the orbital tissues which govern the changes in position of the eyeball in response to change in extraocular muscle tension.

The available literature does not contain any records of either the change in nerve impulses to the extraocular muscles or the change in tension in these muscles during a saccadic movement.

Labyrinthine stimulation, particularly the fast phase of nystagmus, produces eye movements which resemble saccadic movements very closely. Figure 7 shows the fast phase of the nystagmus of a patient with congenital nystagmus and, for comparison, a saccadic movement of equal extent in a normal subject. The two movements show very much the same characteristics.

Accurate records were obtained by Lorente de Nó [13] of the changes in muscle tension during nystagmus. The fast phase is characterized by a very rapid rise in tension of the agonist, maximum tension being achieved in 25 to 30 msec. There is a concomitant relaxation of the antagonist, but the two effects are not always in strict synchrony.

Szentágothai,[14] in a recently published monograph, shows records of the contraction of the eye muscles induced by stimulation of the labyrinth. The reaction time is only 10 msec., and the maximum contraction is reached in 20 to 25 msec. During a tetanic block (250 stimuli per second) applied to the third nerve nucleus, the eye muscle very quickly reaches its peak tension, which is held during the whole period of stimulation. The peak contraction is reached without overshoot. Cooper and Eccles,[15] in their classic paper, showed that the contraction time of an extraocular muscle for an isolated twitch is only about 7 msec., by far the shortest of any muscle in the body.

McIntyre [16] studied the action potential of the nerve serving the extraocular muscle and the tension of the muscle during caloric nystagmus, recording the two simultaneously. He finds, as did Lorente de Nó, a rapid contraction of the lateral rectus muscle during the fast phase and a gradual relaxation of the tension in this muscle during the slow phase if the nystagmus is in a nasal direction for this eye. Similar changes, *mutatis mutandis*, were seen if the nystagmus was in the opposite direction. Evidence from several directions thus indicates that during the fast phase of nystagmus there is an active contraction of the one muscle, reaching a high level of contraction quickly and retaining this level until it is gradually reduced during the slow phase. Meanwhile, the opposing muscle is relaxed during the fast phase and gradually increases its tension during the slow phase. Earlier work on the eye muscles during nystagmus by McCouch and Adler [17] has indicated this, and Sherrington had originally demonstrated it for skeletal muscle. Recent electromyographic data by Pulfrich [18] seem also to agree with this view.

It is important to clarify this point, since the acceleration curve in Figure 5 lends itself to other interpretations, which have occasionally been put forward (Stetson [19]). In such a view the positive part of the acceleration curve is due to active contraction of the agonist during the movement. Later during the movement the agonist ceases to contract, and after a variable time, depending on the extent of the movement, the antagonist, by active contraction, stops the movement. This is often called a ballistic movement. All available evidence is opposed to such an interpretation. Making the assumption that saccadic movements and the fast phase of nystagmus are alike, all records show a relaxation of the opposing muscle throughout the fast phase. At the same time there is a rapid increase presumably to a steady high level of contraction in the agonist. Such a view represents a full justification of the concept of reciprocal innervation.

Applying this to saccadic movements, one can then say with a considerable degree of justification that they are brought about merely by a change in torque which the extraocular muscles are applying to the eyeball, the latter coming to rest in a position representing an equilibrium of the forces applied. It is helpful to think, and is almost certainly correct, that the movements are triggered off as a unit in the central nervous system and that the change in torque takes place very quickly, the eye coming to rest

in a position determined by the forces opposing the motion. A motion such as the one illustrated in Figure 4 can be described, with some degree of generality, by an equation of the form

$$A\ddot{\theta} + F(\dot{\theta}) + K(\theta) = f(t)$$

which states that if a forcing function $f(t)$, a function of time, is applied to the eye, it is opposed by the inertia of the system, a friction term which is a function of the velocity, and a spring term, which is a function of the displacement θ.

The simplest linear system of this kind is one in which the friction is proportional to the velocity and the spring force is proportional to the displacement from a given position. This brings the left-hand side of the equation into the following form

$$A_2\ddot{\theta} + A_1\dot{\theta} + A_0(\theta - \theta_0)$$

It is not difficult to assign physical meaning to the constants A_2, A_1 and A_0.

A_2 is the moment of inertia of the eyeball; A_1 is the coefficient of friction which the eyeball encounters in the course of its movement in the orbit; A_0 is in a large measure an expression of the force with which the relaxed muscle opposes the extension which the other muscle brings about in moving the eyeball to the new position.

In the solution of this equation we make a further assumption, this time about the muscular forcing function. While all the references cited seem to agree that a movement like a saccadic movement is brought about by a quick change in tension of the muscles, it is unlikely that this change is completely instantaneous. In fact, it is quite likely to take 20 to 30 msec. before the peak contraction is reached. This is still only a fraction of the duration of the whole movement, which may last 60 msec. or more.

In making the assumption that the change in torque is instantaneous, we shall arrive at physical constants which will overestimate the contribution that these mechanical factors of inertia, friction, and elasticity will make to the movement. It will be shown that even then they are small enough not to contaminate our records too much, and that we may regard practically all phenomena which our eye movement records demonstrate as genuine changes in innervation and hence as accurately reflecting the central nervous response to our stimuli.

For a saccadic movement we can then write the following equation:

$$A_2\ddot{\theta} + A_1\dot{\theta} + A_0\theta = K \qquad \cdots\cdots (1)$$

K being a constant. The problem is to evaluate the constants A_2, A_1, and A_0 from curves such as the one shown in Figure 5.

It is of value to introduce the following parametric form of Equation 1 (Trimmer [20]):

$$\frac{\ddot{\theta}}{\omega_n^2} + \frac{2\zeta\dot{\theta}}{\omega_n} + \theta = K \qquad \cdots\cdots (1A)$$

WHERE

$$\omega_n = \sqrt{A_0/A_2}$$

$$\zeta = A_1/2\sqrt{A_0 A_2}$$

The solution of Equation 1A consists of two parts, the complementary function, which is the solution to the equation

$$\frac{\ddot{\theta}}{\omega_n^2} + \frac{2\zeta\dot{\theta}}{\omega_n} + \theta = 0 \qquad \cdots\cdots (2)$$

and the particular integral, which takes into account the particular type of forcing function $f(t)$.

The solution of Equation 2 is

$$\theta = e^{-\zeta\omega_n t}\left(\theta_i \cos\omega t + \frac{\zeta\omega_n\theta_i + \dot{\theta}_i}{\omega}\sin\omega t\right) \cdots (3)$$

and expresses the manner in which the steady state of response to the forcing function is reached. θ_i and $\dot{\theta}_i$ are the values of θ and $\dot{\theta}$ when $t = 0$.

The constants ω_n and ζ characterize the system and approximate numerical solution (Trimmer [20]) of a number of curves of the type of Figure 4 have yielded approximate values as follows:

$$\zeta = 0.7$$
$$\omega_n = 120$$

A description of the significance and use of these parameters is given in modern discussions of servomechanisms (Fitts [21]; James and associates [22]).

It must be fully understood that the assumption underlying the use of Equation 3 is that we are, in fact, dealing with a linear system. Unfortunately, there is evidence that the oculomotor system does not fully fit this description. In a linear system the relation between maximum velocities in the responses to step stimuli of different extents should be linearly related to the stimulus. Figure 6 shows that this is not so in the system under discussion here.

For the time being the nature of the nonlinearity remains obscure. It is probable that, for saccadic movements of short extent, lack of instantaneity of onset of changed torque produces a high degree of "guiding" over a considerable proportion of the whole movement.

A very likely cause of the nonlinearity is a friction term proportional to the square of the velocity rather than the velocity itself, a formulation often used when dealing with friction within a fluid (Stoker [23]). It would, for instance, explain the fall-off from linearity of the maximum velocity curve of Figure 6, since this type of friction would progressively militate against the attainment of high velocities.

Again, the specification of a spring constant may be too simple an assumption. Guth [24] shows a tension *versus* extension curve of muscle which is exponential; according to this, the tension to be overcome in extending a muscle by a given amount would vary with the initial extension. Since the percentage extension produced by even a large eye movement is relatively small, this consideration is probably not an important one.

The nature of the central assumption in this derivation, however, that is, the assumption of a step increase in torque, insures that numerical values of ω_n and ζ arrived at by its use will always exaggerate the contribution of the purely mechanical factors of inertia, friction, and elasticity.

In those cases in which the forcing function is a constant or a constant rate of change, i. e., in the case of a step or a step-velocity forcing function, Equation 3 is

an expression of the deviations of the system from the position which the function would compel it to assume in the absence of these mechanical opposing forces.

The formulation presented here would give the maximum error due to these mechanical factors, and if we make this allowance for these we can deduce with a fair degree of certainty the nature of such forcing functions from the eye movement records.

Equation 3 represents a periodic function, and if $\zeta\omega_n$ is positive and real, it has an amplitude decreasing with time.

Substituting the approximate values for ζ and ω_n obtained earlier and applying Equation 3 to the case of a forcing function applied to the eye which will, when the

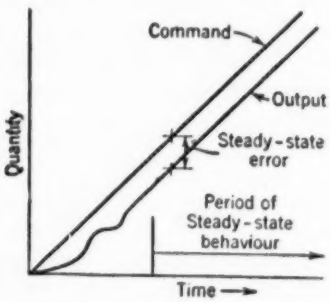

Fig. 8.—Relation between suddenly applied constant velocity input and the output for a hypothetical system with characteristics similar to those postulated for the eyeball in the orbit (after Brown, G. S., and Campbell, D. P.: Principles of Servomechanisms, John Wiley & Sons, Inc., 1948).

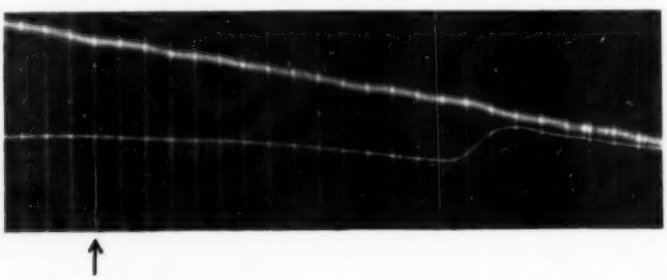

Fig. 9.—Onset of a steady constant velocity movement in the eye. About 180 msec. before arrow, a spot moving with constant velocity (heavy trace) appeared in the subject's field of view. Note gradual assumption by the eye, with oscillatory changes, of constant velocity ("steady state"), which is reached 40 to 50 msec. before the saccadic movement. The latter compensates almost exactly for "steady-state error." Vertical lines indicate 10 msec. time intervals.

transients have subsided, cause the eyes to move with a velocity of 20 degrees per second, we find that the transients are small. Within 35 msec. of the onset, the transients will have an amplitude of 2 minutes, and within 55 msec. they will have an amplitude of 36 seconds. This means that the maximum error at these times as counted from the onset of the forcing function will not exceed the values given.

The exact shape of the response curve can be deduced from an analysis of the equation. Schematically it would look like Figure 8, reproduced from Brown and

Campbell.[25] Comparison may be made with Figure 9, which is taken from an actual record in which a steadily moving stimulus was presented to the eye about 180 msec. before the arrow.

The trace of the corneal reflex of the eye clearly shows the transition period between zero velocity and a steady velocity which is maintained for about 50 msec. before the steady-state error, including a difference in zero position, is compensated for by a saccadic movement.

The transient period in the record is characterized by oscillatory changes, and the constant velocity is reached somewhat more slowly than this formulation would predict for a step velocity input. One is probably entitled to conclude that the latter assumption is too idealized.

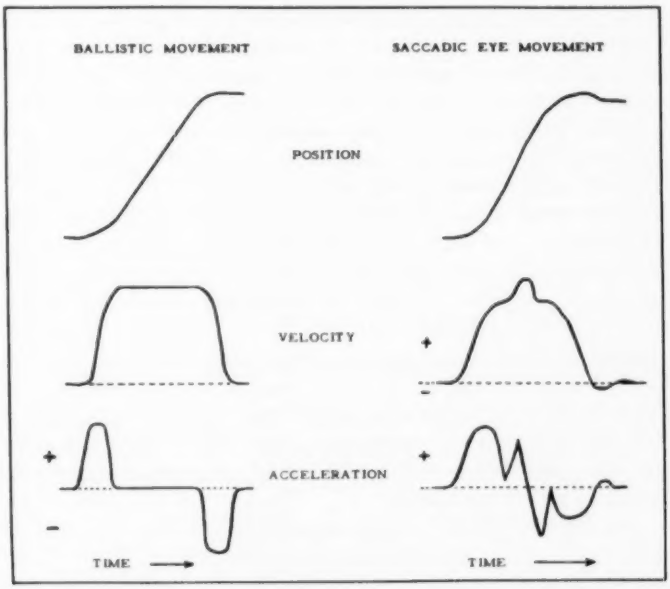

Fig. 10.—Schematic diagram of position, velocity, and acceleration changes during a hypothetical ballistic movement (left) and a typical saccadic eye movement (right).

In general, then, we may conclude that for a reasonably slowly changing forcing function the eye follows the forcing function with considerable fidelity.

It is of interest to compare the actual position, velocity, and acceleration characteristic of a saccadic movement with those to be expected on the basis of the assumption of a ballistic movement. The left-hand side of Figure 10 gives in a schematic way these curves based on the assumption that a movement is started and stopped by sudden and individual bursts of contraction of the agonists and antagonists respectively. The right-hand side shows the curves actually obtained. The movement is obviously not stopped in this manner, since the negative acceleration comes on relatively early in its course.

Considerable variations exist in the details of the acceleration curve of various movements even of the same extent in one subject. In their general features, how-

ever, they are quite alike, and almost all of them show a second burst of positive acceleration. It is likely that this doubling of the positive part of the acceleration curve is due to some small degree of asynchrony in the onset of the contraction of the agonist and the relaxation of the antagonist. This was found by Lorente de Nó [13] to occur in the fast phase of nystagmus.

In connection with the mathematical formulation, it is of interest to note that the root mean square error of the response of the system to a step stimulus would be just about minimized in a system which has the characteristics we have found it to possess. This means that the mechanical system of the orbit works in such a way as to reduce to a minimum the total error involved during the process of shifting from one position to another.

On the whole, the present findings are best explained by postulating the existence of a one-to-one relation between innervation sets to the extraocular muscles and positions of the eye in the orbit. A saccadic movement would then be no more than a practically instantaneous change-over from one innervation pattern to another, and this would occur as a unitary phenomenon, in which instructions for all necessary changes in muscle tension are issued and effected simultaneously, the eyeball coming to a stop in the equilibrium position dictated by the new forces applied to it.

Experimental data supporting this view are contained in a recent paper by Adler.[26] Recording the electrical activity from a lateral rectus muscle in the intact human, Adler and his co-workers found that this activity varies with the position of the eye. When the eye is moved from one position to another, there is a change-over from one pattern of amplitude and frequency to another, this change-over preceding the actual movement by a brief interval.

Furthermore, the identification of eye position with innervation set to the extraocular muscles is in accord with the theory of visual interpretation of the environment proposed by Ludvigh.[27] In such a view, proprioception, so far as it can be shown to exist, would not interfere, if interpreted as a parametric feedback system,[28] with the central role of impulse pattern as the correlate of eye position and of a change in impulse pattern as an eye movement.

SUMMARY AND CONCLUSION

The experiment was designed to study the nervous and muscular mechanisms subserving saccadic eye movements. To achieve this there was developed a method of photographically registering horizontal eye movements with a precision of about 1 msec. in the time dimension and about ⅛ degree in the dimension of the eye movement.

The response to an instantaneous displacement of a small light spot from one position in the visual field to another one in the same horizontal plane consists of a saccadic movement. Such a movement, when studied with the high magnification in the time dimension which the resolving power of the instrumentation permitted, shows certain characteristics not previously described: a high degree of simultaneity of onset of the movement in the two eyes, a rapid acceleration to a maximum velocity which is a nonlinear, monotonically increasing function of the extent of the movement, and a significant overshoot and minute oscillations around the final position.

It is concluded from the present findings, and in the light of physiological evidence from other sources, that a saccadic movement is initiated as a single, unitary

step by means of simultaneous changes in innervation to each of the eye muscles involved. This produces a change in the tension of the various muscles, which may be considered to be effected extremely rapidly. The eyeball then assumes a new position in the orbit which is dictated by the net torque produced by the changes in muscle tension and the forces opposing it—friction, inertia, and elasticity. A mathematical treatment of an idealized physical system of such characteristics suggests that these purely mechanical orbital factors permit the eyeball to follow movement patterns imposed on it with considerable fidelity.

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ELECTRORETINOGRAM IN NYCTALOPIA

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THE PRESENCE of distinct defects in the electroretinogram (ERG) in the varying forms of night blindness has been well documented in recent reports. The most conspicuous changes have been recorded from frank cases of primary pigmentary degeneration of the retina. In these cases the tracings are usually extinguished or greatly reduced in amplitude.* A recent article in the Japanese literature [4] describes similar but less marked changes in Oguchi's disease. Bornschein and Vukovich [5] have observed subnormal recordings with avitaminosis A, and definite changes have also been seen in cases of congenital night blindness without fundus change.† This latter form of nyctalopia appears to us to be of more interest than other forms. The existence of clear-cut alterations is of pertinent significance when clinically evaluating alleged night blindness—especially in the military service. In the past such patients have been frequently looked upon as psychiatric problems, if not actually designated as malingerers. Although psychophysical techniques can be employed, they are extremely laborious and are still, by and large, strictly subjective methods of examination. Objective physiological methods may now be at hand to corroborate subjective or psychophysical findings.

Electroretinograms of congenital nyctalopes seem to display only photopic components, whereas the response of the normal eye is usually complicated by the intrusion of scotopic potentials. It may be mentioned in this conection that some investigators attribute a large a-wave to cone activity [9] while others regard a smaller a-wave followed by a positive x-potential as being more typical photopic.‡ Both predominantly negative and predominantly positive responses have been observed in the study of the ERG of the congenital nyctalope.§ A moot question is whether these differences in the appearance of the electroretingogram result from differences in the procedures of various laboratories or whether some night-blind patients have ERG's which are different in form from those of other patients.

In this report electroretinograms are described for patients manifesting several kinds of night blindness. However, special attention has been given to subjects with congenital night blindness without fundus change.

Army Medical Service Graduate School (Dr. Armington) and Walter Reed Army Medical Center (Dr. Schwab).

Read before the Section on Ophthalmology at the 103rd Annual Meeting of the American Medical Association, San Francisco, June 22, 1954.

* References 1 through 3.

† References 2 and 6 through 8.

‡ References 10 and 11.

§ References 2 and 6.

METHODS OF PROCEDURE

In the present study both electrical and psychophysical measures were made. The technique was similar to that described by Riggs and his associates.‖ A visual stimulator presented the subject with test flashes of selected intensity and wave length. Potentials were obtained from the eye with a silver-silver chloride electrode mounted in a contact lens and were recorded with a Grass ink-writing electroencephalograph. The indifferent electrode was worn on the forehead.

Visual Apparatus.—The same stimulator was used both to elicit the ERG and to make psychophysical observations. The essential arrangement is shown in Figure 1. Light from a tungsten ribbon filament was collimated, passed through a series of interchangeable neutral density and color filters, and brought to a focus in the plane of a shutter. The rays then diverged, were again collimated, and were brought to a second focus at the observer's pupil. The Maxwellian view, thus obtained, presented the observer with a uniform test field, the diameter of which was limited by

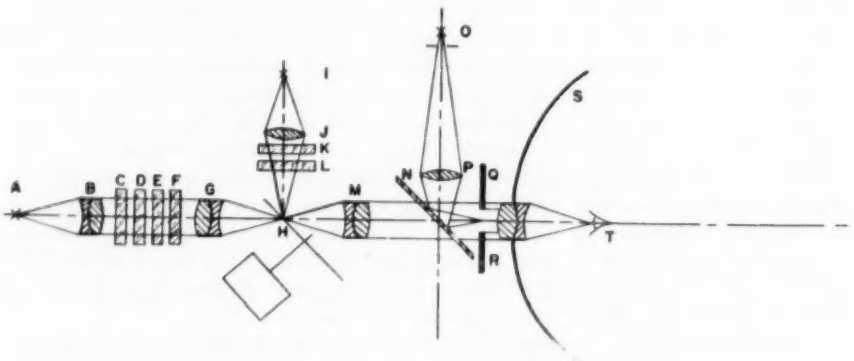

Fig. 1.—Main stimulation system. *A*, source lamp; *B*, collimating lens; *C*, *D*, *E*, *F*, interchangeable neutral density and interference type color filters; *G*, lens; *H*, sectored disk used for flicker photometry; *M*, lens; *N*, unsilvered mirror; *O*, fixation light; *Q*, adjustable diaphragm; *S*, surround or adaptation screen; *R*, final lens; *T*, observer's eye; *I*, auxiliary flicker lamp; *J*, lens; *K*, *L*, neutral filters. When single flashes are used the flicker vane, *H* is removed, and a photographic shutter is mounted in its place. Mirror, *N*, reflects the image of the fixation lamp filament, *M*, into the main optical path.

a diaphragm mounted immediately behind the final lens of the system. The diaphragm could be set so that the stimulus subtended either 30 or 5 degrees at the observer's eye. The observer's head was steadied with a biting board, and a red fixation point, reflected by unsilvered mirrors into the center of the stimulus field, assured proper direction of the eye.

Light adaptation was effected by having the observer view a uniform matt-white screen having a luminance of 2 foot-lamberts. This screen was mounted concentrically about the final lens of the system.

On most occasions a photographic shutter delivering single 0.01-second flashes was employed. Some work, however, involved flicker photometry, and for this

‖ References 12 and 13.

purpose a motor-driven sectored disk or flicker vane was substituted for the regular shutter. White light from an auxiliary lamp was projected upon the magnesium oxide-coated surface of the vane. As the vane rotated, the eye was presented alternately with white light from the auxiliary lamp and colored light from the main stimulus system.

All lamps were powered with direct current. The main stimulus lamp was operated at a temperature of 2500° K. The interference type color filters which were used were calibrated so that the spectral composition and the relative energy content of the light transmitted by each was known when the lamp was operated under these conditions.

Subjects.—The subjects for this work consisted of two patients who manifested a congenital type of night blindness without fundus change, three patients with retinitis pigmentosa, two patients with myopia who claimed impairment of night vision, and one normal subject. Each subject had a complete history, general physical examination, and detailed ophthalomological examination, including refraction and visual field determination.

Subject 2, a 31-year-old white male sergeant, had complained of night blindness since childhood. One brother had a similar difficulty. The patient's true condition was not appreciated until entry into the service in 1942, when he wrecked a truck during black-out maneuvers. Cursory examination at that time leaned toward a functional etiology, but psychiatric evaluation did not corroborate this idea. He desired to remain in the service, and from then on either avoided duty under conditions of diminished illumination or had other personnel members perform his duty for him. Examination revealed uncorrected visual acuity of 20/30, J-1 in the right eye and 20/40, J-1 in the left eye. This could be corrected to 20/25, J-1 in both eyes, with a —0.50 D. sph. O.D. and a —0.75 D. sph. O.S. Color vision was found to be within normal limits using the Ishihara charts, but the Farnworth-Munsell 100-hue test gave some evidence of tritanomaly. The intraocular tensions, pupillary reactions, associated extraocular movements, and slit-lamp examination were all normal. The fundi appeared normal throughout, without evidence of vessel attenuation or pigment deposition. Visual fields were normal to 3/330 white under ordinary illumination but immediately constricted to within 10 degrees of fixation when the illumination was reduced to less than 1 f.-c.

Subject 3, a 20-year-old white private, gave a guarded history of some difficulties with vision at night as a civilian, but his first real difficulty arose during night problems in basic training. Patient's only sister was said to have trouble getting about in the dark. Patient's only brother had no difficulty in this respect. Uncorrected visual acuity was 20/15, J-1 both eyes. The color vision as measured by the Ishihara chart was within normal limits, but anomaloscope and 100-hue tests gave an indication of deuteranomaly. Intraocular tensions, pupillary reactions, associated extraocular movements, and slit-lamp examination were all within normal limits.

Examination of the fundi was completely within normal limits without evidence of vessel attenuation or pigment deposition. Visual field examination revealed normal fields to 3/330 white, but these fields constricted to within 20 degrees of fixation upon reduction of the illumination to less than 1 f.-c.

The three retinitis pigmentosa subjects all presented visual acuities within the normal range. These cases were selected so that there was no significant degree of ametropia present. The lenses were clear, and the fundi revealed advanced involvement of the retina with typical bone spicule type pigmentation. The discs were atrophic and the vessels attenuated. The visual fields in all cases were constricted to within 10 degrees of fixation under normal illumination.

The myopia of the subjects used in this study was of moderate degree (—4.00 to —8.00 D. sph.) and their ophthalmic examinations were otherwise within normal limits. Visual field examinations revealed some slight peripheral constriction under normal illumination to 3/330 white but no further constriction upon reducing the illumination.

Procedure.—Night blindness was established in the two patients without fundus changes by a lack of the scotopic section of the dark adaptation curve (Fig. 2). The procedure was as follows: The subject was first adapted for 10 minutes to a centrally fixated white field of 30 degrees diameter having a luminance of approximately 10,000 foot-lamberts. This was provided by holding open the shutter of the main stimulator. The light was then extinguished, and as dark adaptation proceeded, the subject was presented with blue test flashes having a peak wave length value of 465 mμ. The test flashes had a diameter of 5 degrees and were also centrally fixated.

Four different measures of spectral sensitivity were made with each of the idiopathic nyctalopes and were compared with similar measures obtained from a normal subject. These were (1) electrical sensitivity with the eyes light-adapted, (2) electrical sensitivity with the eyes dark-adapted, (3) psychophysical sensitivity with the eyes light-adapted, and (4) psychophysical sensitivity with the eyes dark-adapted. Light adaptation was produced by viewing the 2-foot-lambert adaptation screen continuously for at least 10 minutes prior to and during actual experimen-

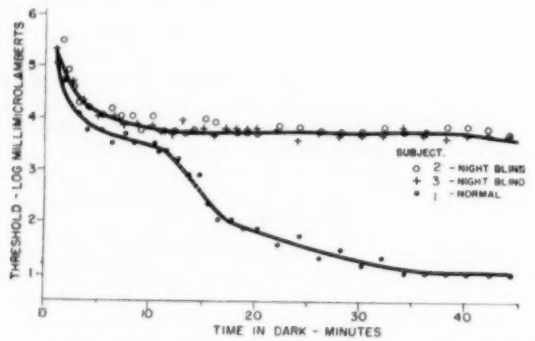

Fig. 2.—Course of dark adaptation in a normal (Subject 1) and two night-blind eyes (Subjects 2 and 3). Night-blind observers fail to show the second, or scotopic, portion of the dark adaptation curve.

tation; for dark adaptation the subject remained in complete darkness for at least 45 minutes before any test flashes were given. Psychophysical determinations with the dark-adapted eye were based upon the absolute threshold, while flicker photometry was used with the eye light-adapted. Spectral sensitivity of electrical data were based upon a criterion height of response of 20 μv. In all cases the actual spectral computations were carried out in accordance with the procedures described by Riggs, Berry, and Wayner.[12]

The ERG alone was investigated in the case of the patients with retinitis pigmentosa and in the case of the myopes. For both a number of red and white flashes of selected intensities were administered under conditions both of light adaptation and of dark adaptation. The resulting responses were compared with those of the normal eye obtained under the same conditions.

All test flashes except those used to obtain dark adaptation curves subtended 30 degrees at the observer's pupil.

Recordings from two congenital nyctalopes without fundus change are shown in Figure 3. Subject 2 has a large negative a-wave and only a small x-wave. On the other hand, Subject 3 shows a much smaller a-wave and a large, more nearly normal x-potential. The shape of each subject's response was not altered with dark adaptation or with variations in the wave length of the stimulus. Although the vision of these two observers appeared to be the same in other respects, their ERG's were quite different in form under all experimental conditions.

Measurements of the amplitude of response as a function of stimulus intensity are found for a few typical cases in Figure 4. With Subject 3, the height of the x-wave was measured in the conventional way,¶ but with Subject 2 no measurable x-wave was exhibited. Hence, measurements of the depth of the a-wave were per-

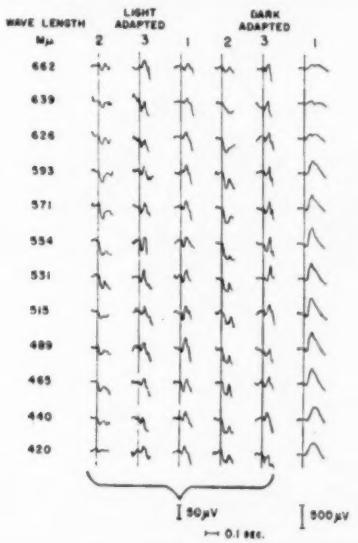

Fig. 3.—Electroretinograms from congenitally night-blind observers. When light-adapted, one subject (Subject 3) has an x-wave response much like that of the normal eye (Subject 2). The other (Subject 2) exhibits a large negative potential followed by an unusually small x-wave. With dark adaptation the night-blind responses increase only slightly in amplitude and are unchanged in wave form, but the normal response exhibits a very marked increase in height as well as a broader wave form. Note that a different calibration has been used for the normal, dark-adapted eye. Responses to different wave lengths show a difference in amplitude but not in wave form.

formed in the manner described by Schubert and Bornschein.[6] Both responses increased gradually with intensity and are typical of those which have been previously described for the light-adapted normal eye.[7] Especially the dark adaptation curves are in marked contrast with those of the normal eye, where response is much larger and where the scotopic b-wave dominates the recordings.

The relative spectral sensitivity for both of these subjects and also the normal observer are plotted in Figure 5. The spectral curves of both night-blind observers

¶ References 7 and 13.

are very similar, and no matter whether the eye is light-adapted or dark-adapted or whether the curves are based upon psychophysical judgments or electrical measurements, they maximize close to 550 mμ, thus giving little evidence as to the existence of the well-known Purkinje shift. In contrast, in the case of the normal observer, the electroretinogram and psychophysical measures do show such a Purkinje shift.

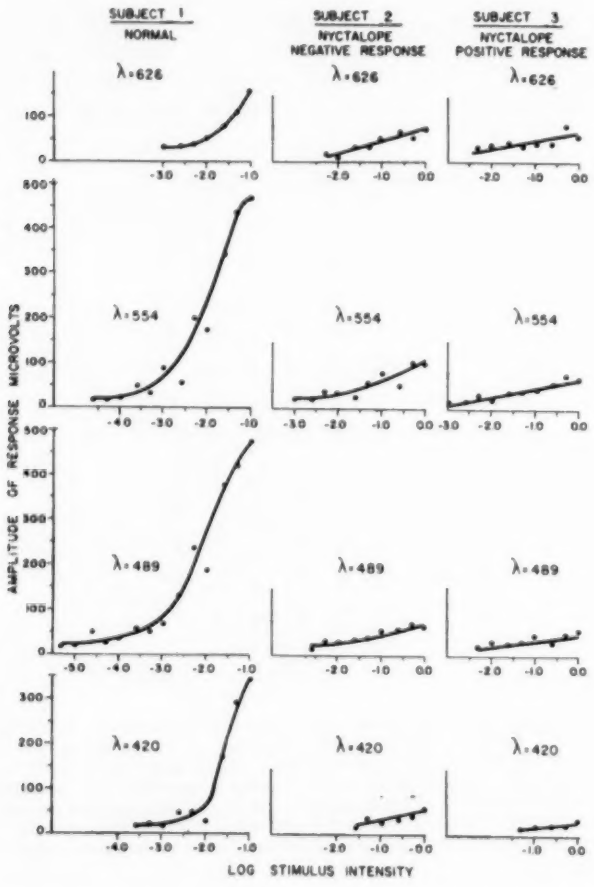

Fig. 4.—Amplitude of response as a function of stimulus intensity with dark-adapted eye. The curves for the two nyctalopes resemble those which are found in the normal light-adapted eye.[7] They are grossly abnormal, however, for this dark-adapted condition.

Typical electroretinograms from three subjects with retinitis pigmentosa are shown in Figure 6. Only one of these patients (Subject 4) showed any clear-cut response, and this was very much reduced in comparison with the normal. No correlation between the degree of retinal involvement, based on ophthalmoscopic observation, and the electroretinographic response was observed.

Decreased acuity under conditions of diminished illumination is often encountered as a complaint in myopic subjects. Electroretinograms from two subjects of this type appeared to be completely within normal limits (Fig. 7).

Our results are largely confirmatory of earlier investigations in bearing out clear-cut deviations from the normal as seen in the electroretinograms of night-blind subjects. Certain points, however, demand further consideration, especially in those cases of congenital night blindness without fundus pathology. Our findings, perhaps, account for the difference in form of the night-blind electroretinograms recorded both by Schubert and Bornschein [6] and by Riggs.[2] Schubert obtained a negative response, while the response found by Riggs was positive. The present finding of both types of response under identical conditions shows that the form of the response depends upon the particular subject used. Congenital night blindness seems to exist in at least two different forms, which may be distinguished with the electroretinogram.

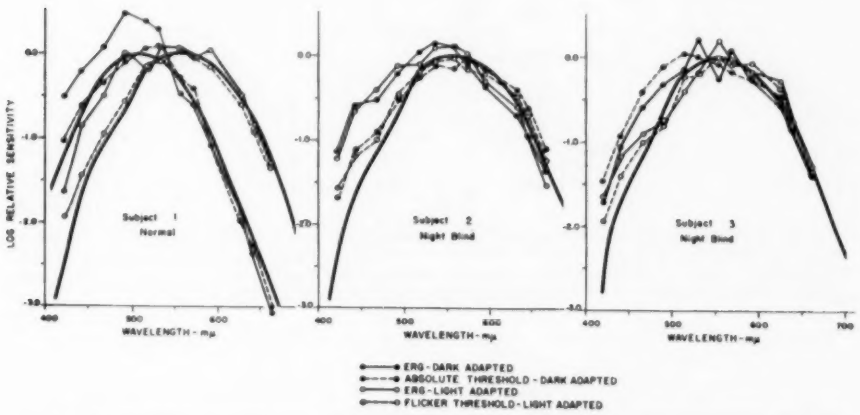

Fig. 5.—Relative spectral sensitivity curves for a normal subject and two nyctalopes. Both the electroretinogram and the psychophysical measure display a shift in relative spectral sensitivity when the normal eye (Subject 1) undergoes dark adaptation. Such a shift is much less evident in the data for nyctalopes. Straight lines connect the experimental points, while the smooth curves are standard luminosity functions shown for purposes of comparison. The one with a maximum at 555 mμ is the ICI photopic luminosity function, while the other (shown only for the normal eye) is the Stiles and Smith [14] mean scotopic function.

A slight increase of blue sensitivity with dark adaptation was noticeable in the spectral curves of Subject 3. While the variability shown by the data of this subject suggests that this observation must be accepted with some caution, a change of this sort was even more conspicuous in a previous study.# Why this increase should be more evident with the earlier subjects and why it should occur at all are still matters of speculation. It does not seem that it can represent the activity of any widespread residual scotopic mechanism. The actual increase in blue sensitivity with dark adaptation is not sufficient to bring the curves into agreement with normal scotopic visibility functions.

On the whole, electrical data had greater sensitivity to the short wave lengths than did the psychophysical. There is a large body of evidence which suggests that

References 2 and 7.

this effect, occurring to a less extent in the nyctalopic than in the normal eye, may be caused by an unusual sensitivity of the ERG to stray and scattered light.[15]

The occurrence of a normal ERG in the case of moderate myopia is not unexpected. There is little evidence that this impairment accompanies actual retinal involvement; furthermore, the absolute threshold of these observers was found to lie within the normal range. A certain degree of myopia is exhibited even by the normal eye under low illumination,[16] and this added to already existent myopia further limits the performance of near-sighted persons. The loss appears to be one of acuity rather than one of absolute sensitivity.

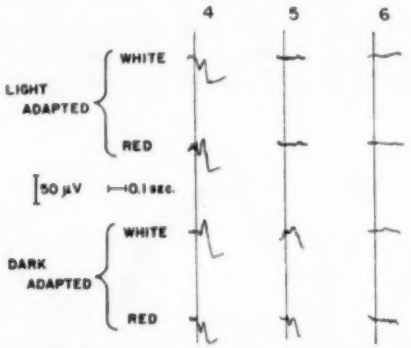

Fig. 6.—Responses from cases of retinitis pigmentosa. One subject (Subject 4) shows a clear-cut response, but this is greatly reduced in amplitude compared with the activity of the normal eye. A second subject gives a response which is still smaller and is apparent only when the eye is dark-adapted. The third subject shows no electrical activity at all.

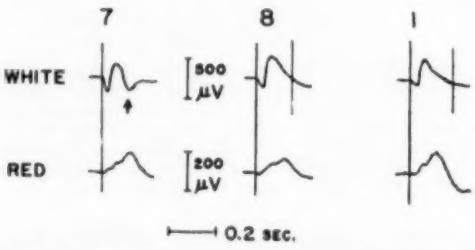

Fig. 7.—Responses from dark-adapted nyctalopic eyes (Subjects 7 and 8). These responses are not distinct from those of the normal eye (Subject 1). The arrow points to an artifact caused by a winking movement.

SUMMARY

Electroretinograms are described which have been obtained from patients exhibiting various forms of night blindness. Those from patients with retinitis pigmentosa were of the typical subnormal and extinguished variety. Those from the congenitally night-blind without fundus pathology exhibited only photopic components. Further, the tracings suggest that this type may exist in two forms. Electroretinograms obtained from myopes with complaints of defective night vision were found to be within normal limits.

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CHOROIDOPATHY

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AT THE 1951 meeting of the American Ophthalmological Society an unusual fundus condition was recorded under the title of choriopathy, characterized by the presence of widely dispersed (although at first only close to the disc), smoky, yellow-gray areas, which increased in number and size from ⅛ to more than ½ disc diameter, varied in shape but were oftenest round or oval, and showed no visible pigment. The fresh spots were the most cloudy and the least defined. When once formed, they persisted but became paler and more sharply demarcated. During the course of the disease a few, small, superficial retinal hemorrhages developed in the macular region, and also a smooth detachment of the lower portion of the retina with a clear subretinal fluid.

Since that time I have made repeated attempts to uncover other cases, by showing the photographs to groups of ophthalmologists and by an exhaustive study of thousands of fundus photographs.

There are three reasons why the disease is reported at this time. 1. While I was in Athens last year, a learned ophthalmologist called my attention to the error in the previous terminology. He was promised that the name would soon be changed from that which seemed euphonious to the accurate, anatomical term choroidopathy. 2. Other reports are desired. This can only be satisfied when colleagues who have seen similar cases record their experiences and publish their photographs. 3. The final objective is to have a forum before which histories of patients with similar patterns may be presented, especially those in whom other fundus changes had been engrafted on or, as occasionally happens, transformed into the definite spots of choroidopathy.

The present exposition is therefore an elaboration of the final objective.

An example of the suggestive pathognomonic spots in which other changes were present was that of Mrs. H. O., 62 years old. Externally the eyes were normal. Vision in the right eye was 5/70. The disc was clear, with no central excavation. The arteries were both few and narrow. There were a great many soft-appearing, round, or irregularly oval spots widely distributed in the posterior pole. These were all beneath the retinal vessels and showed no pigmentation. In the macular region there was an oval of exudate, measuring 1¼ disc diameter, similar to that often found in senile macular degeneration, with two oblique streaks of superficial pigment. If it were not for the macular pathology, this picture would be identical with that described in the original report.

Read before the Section on Ophthalmology at the 103rd Annual Meeting of the American Medical Association, San Francisco, June 22, 1954.

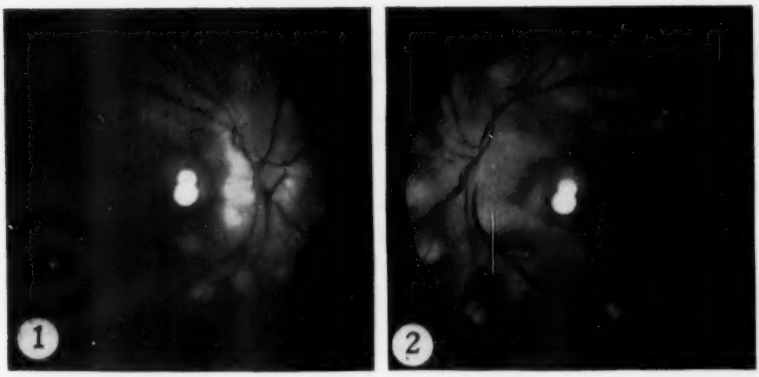

Fig. 1.—Right fundus of the case originally presented, showing widely distributed typical soft spots.

Fig. 2.—Left eye of the same patient. Well-defined isolated spots with a few small hemorrhages over the macula.

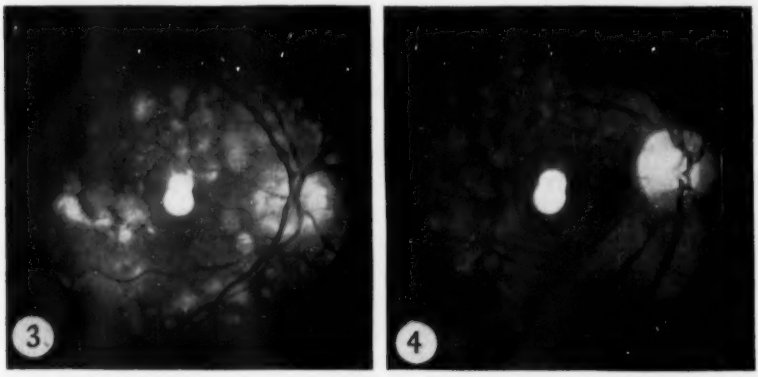

Fig. 3.—The typical spots combined with senile macular degeneration.

Fig. 4.—A broad, almost vertical, band of soft exudates, especially dense in the macular region, and smaller above.

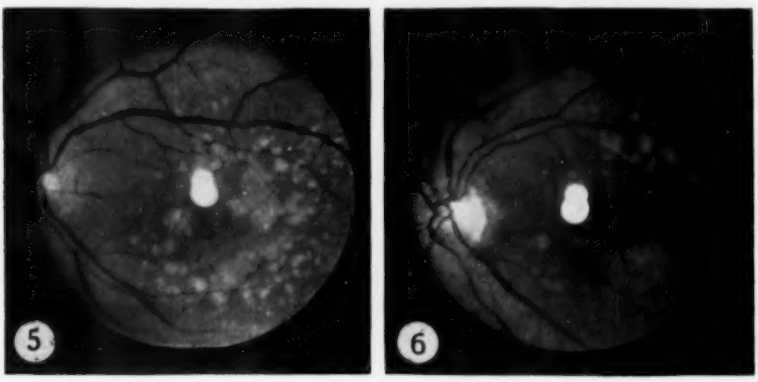

Fig. 5.—Widespread, almost white, isolated and confluent drusen.

Fig. 6.—Six years after Figure 5 was taken. The drusen have entirely disappeared. Several soft spots, similar to those found in choroidopathy, are present.

In the left eye there were flat, soft, round masses varying in size from about twice the width of a vein to ¼ disc diameter. These were fewer than in the right eye but more widely distributed, in a large circumpapillary space. In the macular region there was a bright, oblique streak over a deep infiltration.

Questions suggested are these: Was the macular involvement a separate entity, an essential part of choroidopathy, or the result of senility?

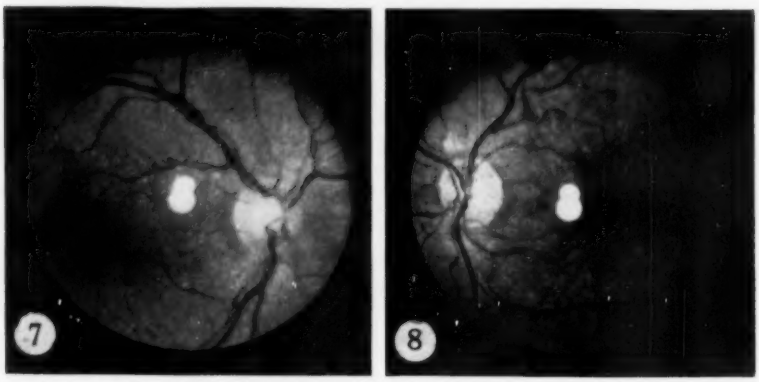

Fig. 7.—Small, sharp, clearly outlined drusen.
Fig. 8.—An almost complete layer of very small drusen.

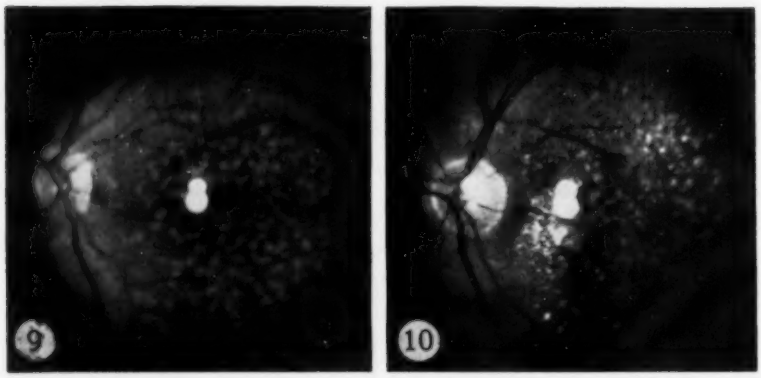

Fig. 9.—Thick, elevated, worm-like drusen confined to a broad zone about the macula.
Fig. 10.—A combined picture of exudates near the disc, innumerable drusen, and a cloudy swelling in the macula.

The time element, both as to the age of the patient when the signs are first seen and as to the duration of the disease, may be an important, even the deciding, factor. We know that in the previously published case changes took place during the period of observation.

Large and small, soft, yellow masses in a broad zone including the macular region and several minute ones close to the disc were present in the right eye of a 63-year-

old woman. These retinal exudates were combined with an early senile macular degeneration. The vision was 4/200.

In a woman aged 65 the vision in the right eye was 20/70, and with +1.00 sph. ⊃ +0.50 cyl. x 180, 20/20+. The disc was well outlined and the arteries uneven in caliber. In a 2-disc-diameter macular region there were several suet-colored, lardaceous, discrete, and confluent masses, over which the retinal vessels passed unchanged in level or width.

That the spots vary in the two eyes was evident in a 69-year-old woman. The sight of the right eye had been failing for several years. The vision was 3/100. There were many soft exudates in apposition to a bright, incomplete ring encircling the macula. Directly above it were similar spots; some were small, while others were almost ¼ disc diameter.

In the left eye the macular degeneration was different, with more pigmentation and fewer exudates. Above and below it there were a number of hard, as well as soft, round, yellowish spots.

A 48-year-old woman had bilateral macular involvement. Vision in the left eye was 20/200, and with +1.00 sph. ⊃ +0.50 cyl. x 180, 20/50. A circle of minute drusen enclosed an irregularly pigmented, degenerated macula. To the temporal side, but still within the circle of the small drusen, were many soft, yellow exudates of the type found in choroidopathy.

When drusen and exudates are combined in a patient with hypertension, it is comparatively easy to distinguish between them. This was well shown in the fundus of a 64-year-old woman whose systolic pressure ranged from 232 to 180 mm. and whose diastolic varied from 110 to 100 mm. Vision in the right eye was 20/200. The retinal arteries were narrow, and the disc was clearly outlined, with a small central excavation. A collection of small, pale drusen was about the disc. Above the macular area were soft, yellow, isolated and coalesced, cloudy exudates.

The study of the next case presents another phase in the interpretation of these spots.

When Mrs. E. W. was 60 years of age, the vision in her left eye was 20/70, and with +1.00 sph., 20/40. In the region about the macula there were numerous almost white, slightly elevated, usually discrete, firm plaques with well-defined borders. Some were confluent, large masses; but most of them were isolated, with very slight disturbance in the pigmentation around them. They ranged in size from the width of a vein to ⅓ disc diameter. The papilla was clearly and distinctly outlined.

It was not until six years later that spots like those of choroidopathy became manifest, coincident with the almost complete disappearance of the drusen. There had been a marked increase in her blood pressure, which was 205/100, and at times 240 systolic. The arteries showed a uniform constriction; the veins were not overly full, although uneven in caliber; there were no hemorrhages. The drusen were replaced by large, soft, yellow-pink masses, distributed in a broad circle. Below the macula, in a ring about the width of the disc, the retina was absent, and over the pale base a branching choroidal vessel was traced.

To stress the differences between colloid masses and choroidopathy spots, a series of the former is exhibited.

The smallest drusen are shown in the right fundus of M. B., a 30-year-old woman, whose corrected vision was 20/20 in the right eye. The oval disc was clear, with normal retinal vessels. A group of fine, discrete, bright yellow dots was in the macular area.

Small, pale, well-outlined drusen were scattered about the macula in the right eye of a 41-year-old woman. The disc was pale and the artery reflex increased. Vision was 20/100.

In a 55-year-old woman with 20/20 vision widely distributed small and medium-sized drusen were about the macula, a common position.

In a 36-year-old man the entire posterior pole was covered by a layer of minute yellow, subretinal drusen.

The vision of the left eye of a 40-year-old woman was 20/30. A considerable number of unusually bright, elevated, punctate drusen with a few very faint pigmented specks were collected above the macula.

Large drusen were beautifully recorded in a photograph of the right eye of a 77-year-old man. The vision was 20/40; with +0.50 sph. ⊃ +0.75 cyl. x 90, 20/30.

In the right eye of a 66-year-old man, a wide central area was almost completely covered by moderate-sized discrete drusen; corrected vision, 20/20.

In a circummacular area, 4½ disc diameter, small and large, soft, guttate, yellow drusen arranged in a geometerical pattern dominated the fundus of a 64-year-old man, who had 20/20 vision.

In a 36-year-old woman a broad zone about the macula was studded with soft, coalesced, whitish-yellow spots, forming long, worm-like ridges. These drusen were, as usual, beneath the retinal vessels.

A 56-year-old man was examined two years prior to this report, when the vision of the right eye was 20/50. At that time there were many soft, yellow, isolated and confluent drusen. Some months later a smoky, cloudy, choroidal infiltration extended about 3 disc diameters beyond the macula. This macular degeneration steadily increased in extent and density, while the spots became less distinct.

In the left eye the vision was 20/100. The spots were distributed beneath the retinal vessels, and later a hazy area developed in the macular choroid with several small, hard-appearing superficial exudates between it and the disc. This was subsequently followed by deep, flat, granular hemorrhages, such as are usually observed in the course of senile macular degenerations. Where the hemorrhages were thickest, the spots were less defined, often completely obscured.

The most important points in the differential diagnosis of drusen and choroidopathy must be very carefully considered. Under certain conditions it is possible to follow the development of drusen. This was made possible in the observation of a patient who first presented with a central serous retinopathy. This subsided and left a few isolated speck-like dots in the macular region, which soon increased in number to form a complete layer. This formation was not the result of the preceding vascular change, for a sheet of drusen soon developed, without any prior visible circulatory alterations, in the left eye.

Drusen may be very small, bright, almost flat, glistening dots, distributed about the macula or disc. They may be few or so numerous as to give the appearance of a superimposed stratum.

There are also larger, translucent, gray-yellow spots above the retinal plane, and combinations of large and small, white, hard-appearing deposits, either widely distributed or localized, which may or may not have edges of granular pigmentation. Confluent soft, gray, cloudy elevations may be arranged in rows or haphazardly distributed.

In choroidopathy the patches at times lose their rounded margin and become jagged, elongated, almost frayed in appearance.

From this review it must be evident that drusen and the spots of choroidopathy are not the same.

In tuberculosis the lesions are fewer; they almost invariably show some pigmentation and, except in the miliary form, are seldom, if ever, as numerous as those in choroidopathy, in which the spots not only remain free from pigmentation but also increase in number and size. In the original case the spots were definitely behind the detached retina and, seen through the fluid, were proved to be in the choroid.

Dr. Albert C. Snell Jr. has graciously permitted me to report on his patient, in whom the fundus lesions resemble those found in our original case.

A woman had pulmonary tuberculosis in about 1930 and at the same time had eye symptoms which she was told were due to tuberculosis of the retina of both eyes. This condition improved after a year and a half under tuberculin therapy. When I first examined her, in 1947, the fundus lesions were extremely numerous, pale, and conspicuously not pigmented. A few of them gave me the impression of recent, but subsiding, activity, that is, resembling chorioretinal inflammatory foci. There were a few vitreous opacities, and in one eye an equivocal aqueous ray was seen with the slit lamp and rare floating cells in the aqueous. There has never been any further evidence of active uveitis. The patient has experienced progressive loss of visual fields as the years have gone by. She now has nothing but a small central island. This defect is not sharply outlined, and there is a spotty residue of peripheral vision with extremely large test objects. In September, 1953, a dark discoloration appeared at the right macula, with reduction of visual acuity to 20/60. This I interpreted as a deep retinal, or possibly subretinal or choroidal, hemorrhage.

Other interesting clinical observations are the development in senile macular degeneration of spots about the macula similar to those in choroidopathy and the possibility that gross drusen may disappear. Occasionally large, soft, only slightly elevated spots look like the exudates in the retinopathy of terminal nephritis or hypertension.

SUMMARY

An ophthalmoscopic curiosity is presented for diagnosis and etiologic consideration, and in the hope that some effective treatment may be suggested.

Reference is made to the original recorded case.

The spots are more generally distributed than the literature suggests.

No factor has been found to be a common denominator, although the influence of age cannot be excluded.

Somewhat similar areas have been observed concurrently with senile macular degeneration and the dissolution of drusen.

Drusen of various sizes are exhibited and their clinical characteristics explained.

As far as is known there has been no pathological report of choroidopathy.

An arresting statement is made by Samuels and Fuchs.[1]

Apparently there also exist in the United States cases of drusen of a larger size which are scattered over the fundus as yellowish discs, some five times as large as ordinary drusen. They may be seen combined with the usual small drusen and also in the midst of senile degeneration. Possibly they are not genuine colloid excrescences but small blebs that are formed by a semifluid that detaches the pigment epithelium. . . . In another case yellowish spots the size of 1/6 disc-diameter made their appearance and after many years could no longer be seen.

Further studies of clinical material must be made. Eventually a pathological report may clarify the situation, but until then interested ophthalmologists will observe and record.

REFERENCE

1. Samuels, B., and Fuchs, A.: Clinical Pathology of the Eye, New York, Paul B. Hoeber, Inc., 1953, pp. 181-182.

USE OF P^{32} AS AN AID IN DIAGNOSIS OF INTRAOCULAR NEOPLASMS

Further Observations

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AND

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PHILADELPHIA

IN A PREVIOUS paper [1] a test using radioactive phosphorus for the detection of intraocular neoplasms was described. The test consisted of injecting 500 μc of P^{32} intravenously. One hour later counts were taken at the limbus of the normal eye in positions 12, 3, 6, and 9 o'clock. The counter was placed as close to the lesion as possible in the pathologic eye. These counts were recorded as the number per minute.

The limbus was selected as a point of reference as opposed to corresponding points of the globe, for such counts showed less variation with the above technique. This point is stressed, for unless the area over the limbus is used as reference points the results are not consistent. From the data obtained with this technique the following conclusions were reported.

1. Neoplasms will concentrate P^{32} in amounts significantly increased over that of normal tissue, and this difference in concentration can be determined if the tumor is within reach of the counter. Lesions in the posterior segment of the globe may or may not be detected, depending on their size and activity.

2. Active inflammatory lesions also will show concentrations of radioactive phosphorus increased over those found in normal ocular tissue.

3. Serous detachments do not concentrate radioactive phosphorus.

4. A concentration of 30% or more greater than the average in the normal eye should be considered a significant uptake with this technique.

From these data it was apparent that the test had to be modified in order to enable one to differentiate inflammatory from neoplastic lesions.

In 1940, Jones and his co-workers [2] injected P^{32} in a series of mice having lymphoma, lymphosarcoma, and mammary carcinoma. The P^{32} content of the various tissues, such as heart, liver, intestine, and neoplastic lesions, was determined. From these experiments it was concluded that P^{32} remains longer in neoplastic tissue than in normal tissue.

Many observers feel that the uptake of P^{32} in the first hour depends on the vascularity and the carbohydrate fraction, while after 24 hours the uptake depends more on the nucleoprotein metabolism of the cells.

Work done under AEC Authority #17818 and CA 20304.

From the Research Department, Radioactive Isotope Division, Wills Eye Hospital.

Read before the Section on Ophthalmology at the 103rd Annual Meeting of the American Medical Association, San Francisco, June 22, 1954.

MODIFIED PROCEDURE

On the basis of the above observations, it was reasoned that if readings were taken at various time intervals one might in this way differentiate between inflammatory and neoplastic lesions. Accordingly, the test was modified so that counts were taken at 1, 6, 24, and 48 hours after the P^{32} injection.

Employment of this test on the first 25 patients indicated the superfluity of the 6- and 48-hour counts. The six-hour count corresponded closely to the one-hour uptake. The 48-hour count was dropped because in many instances the count fell too low for statistical reliability. This decision was also influenced by the patients' complaints of "sore eyes" if many "readings" were taken.

Summary of 123 Cases of Intraocular Pathology

	Total No.	Test		Pathologic Confirmation
		Positive	Negative	
I. Intraocular malignant lesions	26	26	0	19
A. Malignant melanoma	19	19	0	15
B. Retinoblastoma	4	2	2	4
C. Metastatic carcinoma	1	1	0	0
D. Iris	2	2	0	0
II. Inflammatory retinal detachment	13	0	13	0
III. Serous retinal detachment	34	0	34	0
IV. Hemorrhage	10	0	10	0
A. Hyphema	1	0	1	0
B. Vitreous	5	0	5	0
C. Choroidal	4	0	4	0
V. Cataracts	12	0	12	0
A. Senile	3	0	3	0
B. Cataracta complicata	9	0	9	0
VI. Glaucoma	17	0	17	0
A. Primary	1	0	1	0
B. Secondary	4	0	4	0
C. Absolute	12	0	12	9
VII. Iris lesions (benign)	6	0	6	1
VIII. Inflammatory lesions	5	1	4	1

From the data obtained, it became apparent that the definition of what should be considered a positive uptake of P^{32} had to be altered to include the 24-hour reading. The criteria selected to indicate the positive test for malignant neoplasm were as follows:

1. One-hour reading: The concentration of P^{32} in the pathologic lesion should be 30% or more greater than the average in the normal eye.

2. Twenty-four-hour uptake: The ratio of the concentration of P^{32} in the pathologic eye to the average in the normal eye must be greater than the one-hour concentration ratio.

For example, if in 1 hour the concentration was 45% more than in the normal eye, in 24 hours the concentration must be over 45% more than in the normal eye.

To obtain the above data, readings were taken at 12, 3, 6, and 9 o'clock at the limbus and recorded as counts per minute. With this technique enough readings are taken to confer statistical reliability. The average of these readings is designated as X. Enough readings are taken also over the lesion, and the average of these readings is designated as H. The number of readings taken depends on the degree of

variation over a particular area. The greater the variation the more readings should be taken. A minimum of four is advisable. The formula utilized is as follows:

$$\frac{H-X}{X} \times 100 = \%$$ of concentration of P^{32} in pathologic eye as compared with that in normal eye

This modified procedure has now been used in 123 cases with intraocular pathology. The results are as follows:

I. *Intraocular Neoplasms.*—A total of 26 patients with clinically diagnosed or suspected intraocular neoplasms were tested with radioactive phosphorus in this study. Of these, 15 had solid-appearing retinal detachments; in 2 the lesions were manifested by pigmentation and anterior staphyloma, and in 2 more by dark-pigmented lesions of the iris. One tumor appeared to arise primarily in the con-

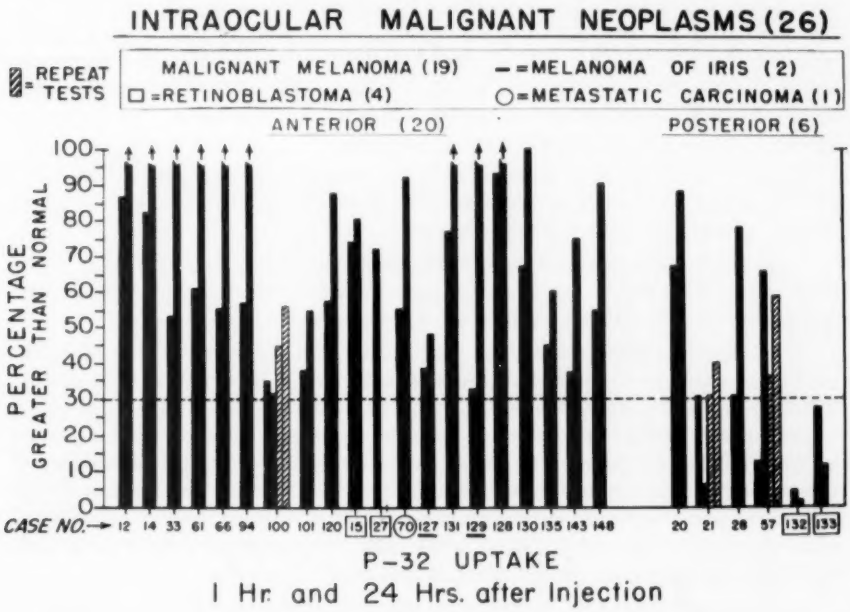

Figure 1

junctiva; four tumors were retinoblastomas; one lesion perforated the sclera and was manifest as a small, darkly pigmented mass approximately 2 by 2 mm., and one presented itself after a keratome incision had been made for a cataract extraction. Of the 15 solid-appearing detachments, 12 proved to be unilateral malignant melanomas by pathologic study. In three cases the pathologic findings are not yet available. One case had bilateral serous detachments with a unilateral solid detachment of the retina in the right eye due to metastatic carcinoma (breast). The last case showed positive results only when the normal limbal readings were taken from the right eye; the left eye failed to give a positive test. A plausible explanation for the failure of the left eye in this case could be that (1) the metastatic lesion was too far posterior to be reached, (2) the metastatic lesion was present but was in an inactive phase of metabolism, or (3) no metastases existed in this eye and serous detachment was coincidental to the retinal detachment in the right eye.

In four cases the test was repeated in one week to one month after the initial study (Fig. 1). Repeat tests were performed when the findings of the test were not in agreement with the clinical diagnosis.

In Case 21 the one-hour reading was "30% greater than normal," and since the ophthalmoscopic picture was so typical of neoplasm, an increase in "percentage greater than normal" was expected. The 24-hour reading failed to corroborate our assumption. Enucleation was delayed and the test repeated in one week. The repeat test revealed a reading over 30% above normal in one hour, with an increase in 24 and 48 hours.

In Case 57 the lesion was in the posterior segment and failed to meet the criteria for positivity in that the one-hour reading was only 13% "greater than normal," even though the 24-hour and 48-hour readings were well above 30%. A repeat test one week later revealed positive 1-hour and 24-hour readings. In order to eliminate error due to the fact that the lesion was posterior, a count was performed approximately 25 hours after the repeat injection with the lateral rectus muscle detached and the Geiger-Müller tube placed directly over the lesion. The difference in count, as would be expected, was much greater.

Case 100 failed to show an increase in "percent greater than normal" 24 hours after injection. Instead of the expected rise, there was a small decrease. A repeat test one month later gave a positive result.

Case 124 failed to show an increase in percentage greater than normal 24 hours after injection. A repeat test performed one week later showed a marked increase in the 24-hour calculation, and therefore a positive test.

It is difficult to explain the above four initial failures. The possibility of failure in the apparatus or the technique must be considered. However, in each case at least one of the two major readings (1-hour or 24-hour reading) was in line with a positive test. If the fault did not lie with the apparatus or the technique, it could be reasoned that the failure was due to the tumor itself; that is, the metabolism of the tumor at the particular time of the test might have been at a minimum. Therefore, there was a state of relative inactivity within the tumor, and its phosphorus uptake resembled the normal tissues of the body. Regardless of theory, the answer to this problem does not present itself at this time.

Of four cases of proved retinoblastoma, two produced positive tests and two gave negative tests. One of the two negative tests is difficult to explain (Case 132). Clinically the tumor looked like a retinoblastoma and appeared to fill almost the entire globe. On section, a large mass was found extending almost from the posterior pole to the disc. Therefore it was felt that our counter was placed close enough to the lesion to pick up the concentration of P^{32} if it was present.

The other negative test (Case 133) can be explained, for the eye was enucleated 24 hours after the injection of P^{32}. Counts were then made over various parts of the globe, and a significant concentration was found near the optic nerve on the medial side. On section, the tumor was found to be located in the area over which the concentration was observed. Thus, it may be reasoned that the probe was too far anterior to the tumor mass.

II. *Serous Retinal Detachment.*—A total of 34 cases with serous retinal detachments were tested with P^{32} (Fig. 2). In no instance was there a positive test. Many cases showed a decreased uptake over the area of retinal separation as compared

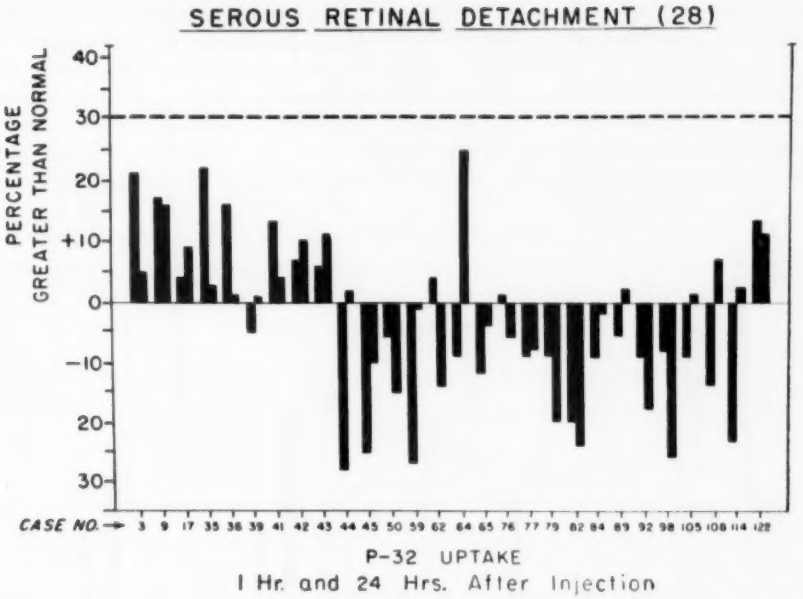
SEROUS RETINAL DETACHMENT (28)
PERCENTAGE GREATER THAN NORMAL
40
30
20
+10
0
−10
20
30
CASE NO. → 3 9 17 35 36 39 41 42 43 44 45 50 59 62 64 65 76 77 79 82 84 89 92 98 105 108 114 122
P-32 UPTAKE
1 Hr. and 24 Hrs. After Injection

Figure 2

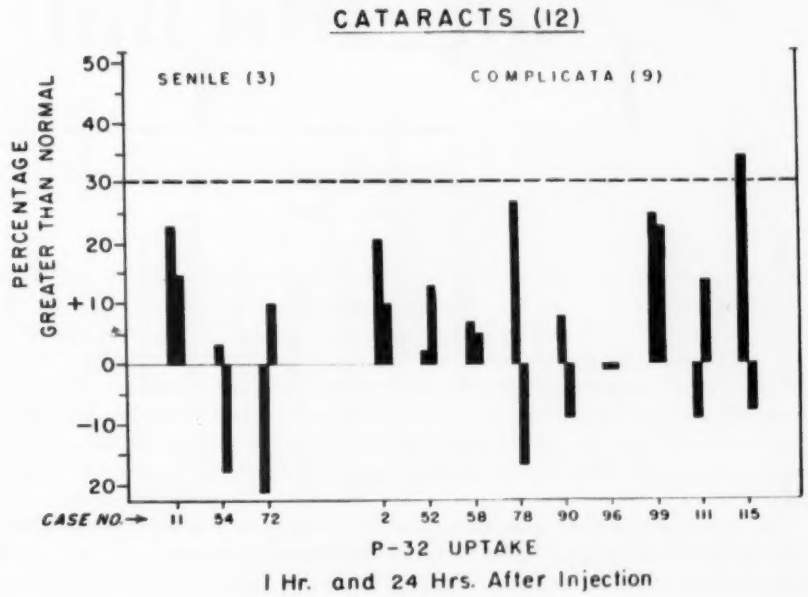

Figure 3

with the normal eye. This may be explained on the basis of less tissue being present at the site of separation and therefore fewer counts per minute being obtained.

Two patients with serous retinal detachment (not represented on Figure 2) who failed to respond to retinopexy were subjected to lamellar scleral resection. Following this, P^{32} uptake studies were performed between one and four months. It was noted that both cases showed a marked uptake of P^{32} one hour after injection over the site of the recent scar, but in both instances there was a decrease in the 24-hour reading.

III. *Cataract.*—There were 12 eyes with cataracts subjected to study with P^{32} (Fig. 3). Of these, three presented senile cataract, and nine, cataracta complicata. In all cases the P^{32} uptake study failed to meet our criteria for positivity, and all

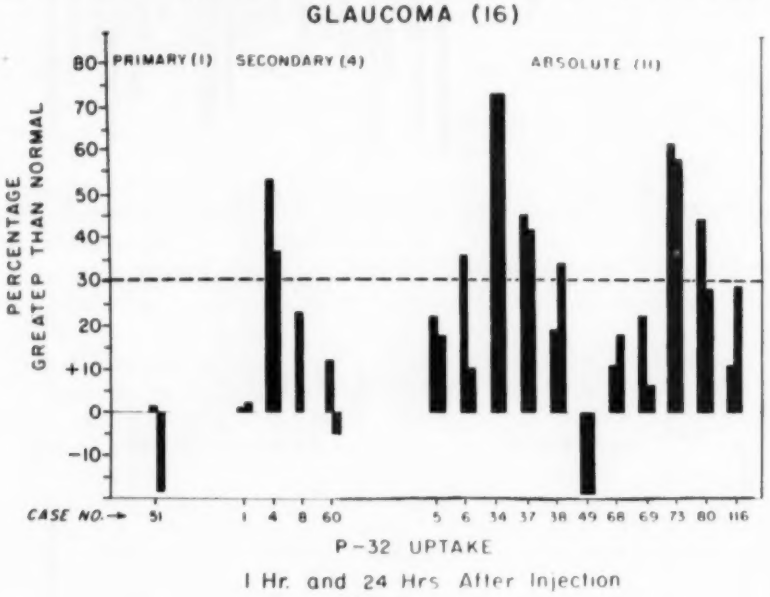

Figure 4

tests were negative. To date, four of these cases have had cataract surgery. Fundus examination failed to reveal any abnormalities in these four cases.

IV. *Glaucoma.*—P^{32} uptake studies were performed in 17 cases of glaucoma (Fig. 4). Of these, the condition in 1 case was diagnosed as chronic simple glaucoma, in 4 cases as secondary glaucoma, and in 11 cases as absolute glaucoma. The cases of secondary glaucoma included two due to inflammation, one to trauma, and one to aphakia. In 8 of the 12 absolute glaucoma cases, the eye was enucleated. All P^{32} tests were negative. Pathologic examination failed to reveal any melanoma in those eyes.

In one case of absolute glaucoma (Case 34) there was a marked initial rise to 73% "greater than normal." In 24 hours there was no decrease or increase in uptake, making this test negative. Pathologic examination of this globe confirmed the clinical diagnosis of absolute glaucoma. No explanation can now be given in this case for the high one-hour reading, though by our criteria this test is negative.

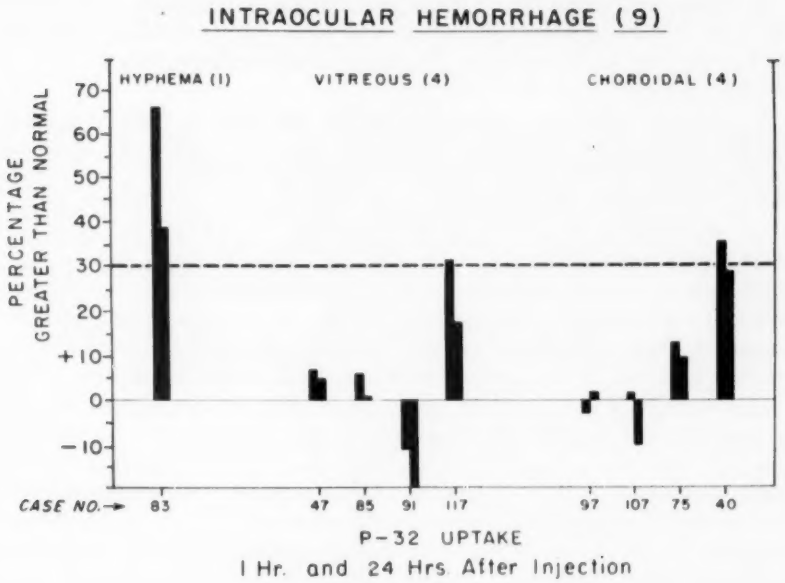

Figure 5

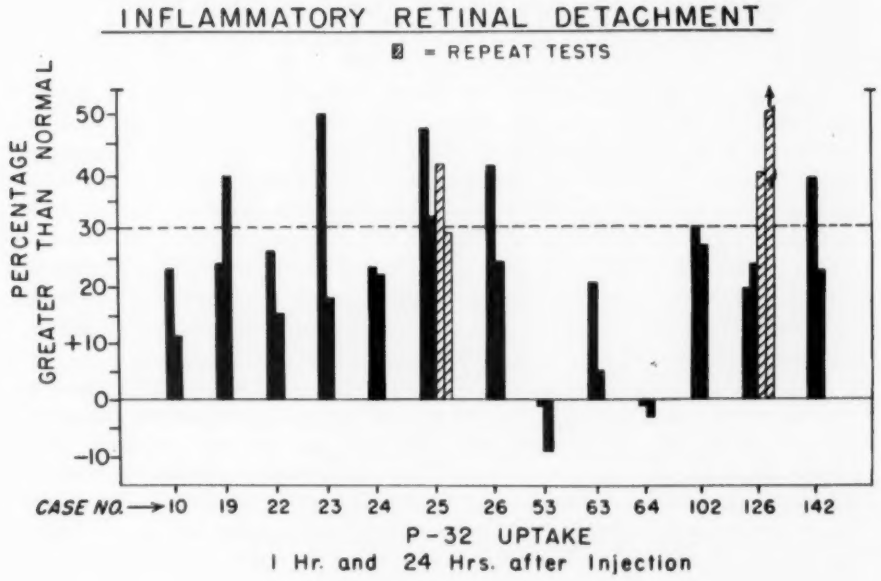

Figure 6

V. *Intraocular Hemorrhage.*—There were 10 cases of intraocular hemorrhage in this series (Fig. 5). Of these, one was of a hyphema, four of vitreous hemorrhages, and four of choroidal hemorrhages. The choroidal hemorrhages were posterior. All tests were negative.

Case 91 was seen by a competent observer, who made a diagnosis of retinal detachment. Between the time the patient was seen in the ophthalmologist's office and his admission to the hospital a vitreous hemorrhage developed. The P^{32} uptake study revealed fewer counts per minute in the pathologic eye than in the normal eye.

VI. *Inflammatory Retinal Detachment.*—There were 13 cases of inflammatory retinal detachment studied (Fig. 6), comprising 7 cases of serous detachment due to inflammation, 2 cases of exudative choroiditis in children, 1 case of proliferative retinitis, 1 case of inflammatory solid detachment, and 2 cases of exudative retinitis in an adult. Three cases showed readings above a 30% rise in one hour. However, there was a decrease in each case in the 24-hour count, indicating negative P^{32} tests.

Case 19 did not show a rise of greater than 30% in one hour and, therefore, was negative according to our present criteria for positivity. It is included here because the test was construed to be positive, owing to our inexperience in interpreting results early in this series. Clinically, the lesion in this case appeared to be a ring melanoma; transillumination confirmed this presumptive diagnosis. However, there were signs of uveitis. P^{32} studies revealed an uptake of less than "30% greater than normal" in one hour, but a subsequent rise in 24 hours and a further increase in 48 hours. It was decided to enucleate the eye. Pathologic examination revealed inflammation of all intraocular tissues, with detachment of the ciliary body, choroid, and retina. Stallard [8] has recently described six cases of annular peripheral retinal detachment, among which this case could possibly be classified were it not for signs of uveitis.

Case 25 was also of interest. A serous retinal detachment of the lower half of the globe was discovered on routine ophthalmologic examination. There had been no recent trauma, but 13 years previously the patient had been struck in the same eye with a baseball. No retinal hole was identified. P^{32} uptake studies revealed a 30% increase in the one-hour reading, with a subsequent fall in 24 hours. At that time this test was considered positive according to the previously reported [1] criteria for positivity. Believing that this test was probably a false-positive one, we postponed surgery and repeated the test one week later. A similar pattern was obtained. Retinopexy was performed, successfully. It was cases such as this one that stimulated the formulation of the new criteria for positivity.

Case 126 is also worthy of report. When first seen, about seven months prior to this report, the patient had a grayish, flat, solid detachment in the superior temporal area of the left eye. The borders were indistinct. No hole was visualized. The clinical diagnosis was inflammation. A P^{32} test was negative. Within six months the lesion appeared to progress, getting larger and more elevated, and some of the areas appeared sharply demarcated. A repeat P^{32} study was then positive. At present the clinical opinion is still divided as to whether the lesion is inflammatory or malignant. To date, the eye has not been removed.

VII. *Inflammatory Lesions Without Detachment.*—Five cases of inflammatory lesions were studied (Fig. 7). Two cases were of posterior uveitis, of which one

(Case 48) was an instance of Jensen's chorioretinitis juxtopapillaria. This lesion was too far posterior to be tested accurately with our present counter.

In three cases the lesion was far enough anterior to be within reach of our counter.

In one (Case 103) the lesion was situated near the ciliary body. It had a dark appearance and was elevated, with numerous blood vessels coursing through it. A tentative diagnosis of a possible malignant lesion was made. This was further strengthened by a positive P^{32} uptake. Nevertheless, opinion was divided as to whether or not the lesion was a tumor or scleritis with a possible staphyloma. The eye was not enucleated, but the lesion appeared to be getting larger. The patient

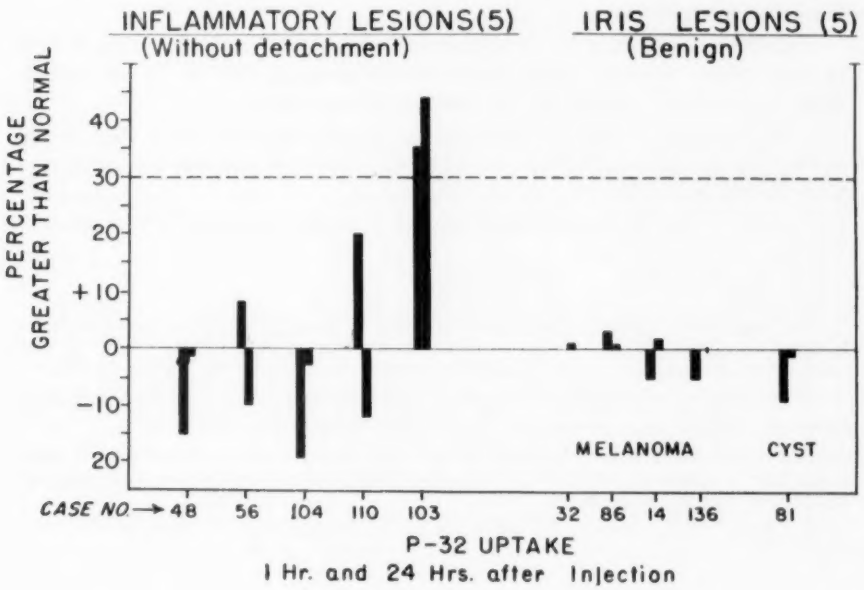

Figure 7

clinically appeared cachectic and the course downhill. This impression strengthened the belief that one might be dealing with a potential malignant growth.

About nine months later the patient died. The eye was made available for pathologic study. On gross section no tumor mass was found, only a somewhat thickened sclera. The histopathologic report is not yet available. Nonetheless, it is assumed that the lesion is inflammatory and the case constitutes the first false-positive result. No ready explanation for this result is apparent. It is felt that only a larger series may suggest an answer.

VIII. *Iris Lesions.*—Six cases with iris lesions were studied, three of which are shown in Figure 7. In four of these cases the lesion was a benign melanoma, while in the fifth it was a posterior cyst of the iris. Tests in these five cases were all negative. The sixth case was that of a 24-year-old sailor with an iris lesion which appeared clinically to be malignant. It contained no pigment and was diagnosed

clinically as a probable leucosarcoma. P^{32} uptake studies were negative. An iridectomy was performed and the tumor removed. Pathologic study revealed a leiomyoma of the iris.

IX. *Choroidal Detachment.*—One case of choroidal detachment was tested with P^{32}. The test was negative. A spontaneous remission of the detachment occurred several weeks later.

SUMMARY AND CONCLUSIONS

From the information obtained on the 123 cases with use of the suggested criteria, the following observations appear justified:

The test is limited in its use to (*a*) subjects with one eye or with bilateral ocular pathology, (*b*) lesions in the posterior segment of the globe,* and (*c*) tumors in the less active metabolic state.

The P^{32} test is positive for a malignant lesion if (*a*) in 1 hour the uptake is 30% or more greater than the average in the normal eye, and (*b*) the 24-hour uptake shows a percentage increase greater than the 1-hour uptake.

A negative test indicated a nonmalignant lesion in approximately 95% of the cases studied. The test, however, was decidedly reduced in accuracy in dealing with retinoblastomas in children.

A positive test was strongly suggestive of a malignant neoplasm in all the eyes studied.

2117 Spruce St. (3)

* A Geiger-Müller probe for the posterior segment is now available, and it is in the process of being evaluated.

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MITOTIC AND WOUND-HEALING ACTIVITIES IN THE RAT CORNEAL EPITHELIUM

Influence of Various Hormones and Endocrine Glands

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CLAES HENRIK DOHLMAN, M.D.
AND
JONAS S. FRIEDENWALD, M.D
BALTIMORE

THE PURPOSE of the present study was to discover whether removal of various endocrine glands or the administration of various hormones and related substances influenced mitotic and wound-healing activities in the rat's corneal epithelium. The methods of assay of these activities previously described * were used in this study.

1. HYPOPHYSECTOMY

Young rats hypophysectomized by the Hormone Assay Laboratory † were obtained for this study. The animals reached our laboratory three days after operation in apparently good condition. Two weeks after operation, six animals were killed and their eyes removed for mitosis counts. The results shown in Table 1 yielded an average count of 53 ± 8 per standard area of cornea. This is less than half the number of mitoses normally found in the same standard counting area and represents a very significant reduction in mitosis number.

Since the number of mitoses might be reduced either by a diminution of mitotic activity or by an increase in the speed of passage of cells through the mitotic process, a second experiment was done, as follows:

The right eye of each of six hypophysectomized rats was removed with the animal under ether anesthesia, and the animals were kept anesthetized for 10 minutes. Previous experiments had shown that in normal animals such anesthesia stops the entrance of cells into mitosis for over an hour but does not interfere with the progress through mitosis of cells already in mitosis at the beginning of the anesthesia. The cells already in mitosis progress steadily, so that, first, prophases, then metaphases, etc., disappear. In normal animals the number of cells remaining in mitosis drops to 10 or 15% of the initial number of 70 minutes, indicating that the average duration of the mitotic cycle in the normal rat is slightly over 70 minutes. In the present experiment, the left eye of each rat was removed 70 minutes after the beginning of the anesthesia. The drop in mitosis count between the right and the left eye was in the same proportion as that in normal rats, indicating that the rate of progress through mitosis was normal in the hypophysectomized animals, and hence

* References 1 and 2.

† 8159 S. Spaulding Ave., Chicago 29.

that the low counts in the unanesthetized animals and in the right eyes of the animals in the present experiment represent a genuine drop in mitotic rate following hypophysectomy.

Three weeks after hypophysectomy an additional five rats were used to assay the rate of healing of pinprick wounds in the corneal epithelium. The rate of healing and the morphology of the healing process were found to be normal.

2. THYROIDECTOMY

Thyroids were removed, under ether anesthesia, from young adult rats weighing 100 to 150 gm. Four to six weeks later the animals were used for mitosis counts, for ether experiments to determine duration of mitosis, and for wound-healing

TABLE 1.—*Effect on Mitotic and Wound-Healing Activities of Rat's Corneal Epithelium of Various Endocrines and Hormones*

	Mitosis Count		Ether Experiment			Wound Healing		
Procedure	No. Animals	Results	No. Animals	Before Ether (R.E.)	After Ether (L.E.)	No. Animals	Results	Comment
Hypophysectomy	6	53 ± 8	6	64	7	5	Normal	Significant reduction in mitosis rate
Thyroidectomy	7	162	7	168	19	8	Normal	Normal
Thyroidectomy plus radioactive iodine	..	...	10	160	33	..	.....	Normal
Thyroxin	6	200	6	157	24	6	Normal	Normal
Thyroidectomy plus parathyroidectomy	5	134	..	...	..	..	.....	Normal
Parathyroid cauterization	2	97	5	154	29	6	Normal	Normal
Alloxan diabetes	8	147	8	142	35	2	Normal	Normal
Alloxan diabetes normal controls	8	161	8	186	28	2	Normal	Normal
Adrenalectomy	7	124	6 Ether and epinephrine 6	118 126	54 22	6	Normal	Diminished adrenergic response to ether
Cortisone	14	Before 139 After 173	8	180	24	12	Normal	Significant increase in mitosis rate
Corticotropin	8	Before 126 After 120	7	120	11	5	Normal	Normal
Heparin	8	Control 112 Treated 126	5	Control 23	Treated 30	8	Retarded	Significant retardation of wound healing

assays. The results, as summarized in Table 1, were all within normal limits. In order to be sure that the thyroidectomy was complete, a second series of rats were operated on in the same way, placed on an iodine-deficient diet for seven days, and then given an intramuscular injection of 15 to 20 mc. of radioactive iodine (sodium radioiodide, I^{131}). Two weeks later these animals were subjected to the ether experiment. No abnormality in mitosis number or in mitosis duration was found.

3. THYROXIN ADMINISTRATION

The following experiments were performed in order to see whether an extremely severe acute intoxication with thyroxin would exhibit an effect on mitotic or wound-healing activities. One cubic centimeter of thyroxin (1 : 1,000) was injected intramuscularly into each of 18 rats. Twenty-four hours later the animals were used for mitosis counts, for ether experiments to determine the duration of mitosis, and

for wound-healing assays. The number of mitoses was slightly on the high side, but not outside the normal range. The duration of the mitotic process and the rate of wound healing were both normal.

4. PARATHYROID REMOVAL

In the thyroidectomies reported above, no special effort was made either to remove or to avoid removing the parathyroid glands. Of 38 animals so operated on, 6 were observed during the next two weeks to show signs of parathyroid deficiency—positive Trousseau sign, muscular cramps, etc. These animals were not included in the thyroidectomy series reported above but were considered to have had combined thyroidectomy and parathyroidectomy. Mitosis counts were done on these animals three weeks postoperatively. One of the animals was acutely sick and apparently moribund at the time of killing and showed very low mitosis counts (20 and 12 in right and left eyes, respectively). Similarly, low counts have been noted by us in sick and moribund animals before, and there seems to be no reason to attribute these low counts directly to the parathyroid deficiency. If this one animal is omitted from the group, the average mitosis count in the 10 corneas of the remaining 5 animals was normal.

In an additional series of animals, destruction of the parathyroid glands was attempted by electrocautery according to the technique of Goldmann.[3] Following this procedure the animals showed variable and inconstant signs of parathyroid deficiency. Two out of 13 showed subcapsular lenticular opacities, and all showed at some time or other a positive Trousseau sign or muscular spasticity. The animals were used three weeks postoperatively for mitosis and wound-healing assays. The results of these tests were within normal limits.

5. ALLOXAN DIABETES

Alloxan monohydrate, 350 mg. per kilogram of body weight, was injected intramuscularly into each of a large series of rats after two days of starvation. The animal's urine was collected on the second day after alloxan administration, and only those giving a 4+ reaction were retained in the experiment. Tests of mitotic and wound-healing activities were made one week after the establishment of the diabetes. The results of these tests were within normal limits.

6. ADRENALECTOMY

Bilateral adrenalectomies were performed on rats under ether anesthesia. The animals were maintained postoperatively on a high-salt diet without administration of adrenocortical hormone. They were used three to four weeks postoperatively for mitotic and wound-healing assays. Mitosis counts in these animals' corneas were within normal limits, but the decline in mitosis numbers 70 minutes after ether anesthesia was much less pronounced than in normal animals. This might be taken to mean that the duration of mitosis in these animals was abnormally long. Previous studies, however, had indicated that the inhibition of mitosis resulting from ether anesthesia was attributable, at least in part, to the release of epinephrine during the excitement stage of ether anesthesia. Since the adrenal glands in these animals had been removed, this adrenergic component of the ether anesthesia was necessarily lacking. The assay of mitosis duration was, therefore, repeated, with the addition of an intramuscular injection of 0.1 cc. epinephrine 1 : 1,000 during the anesthesia.

The mitosis counts under these conditions declined at the normally expected rate. The experiment shows that there is no change in the rate of progress of these cells through the mitotic cycle. It shows also that the conclusion previously reached that ether anesthesia inhibits mitosis in part by an adrenergic effect was correct.

7. CORTISONE

Cortisone acetate emulsion was injected intramuscularly in 5 mg. doses daily for five days into 150 gm. rats. The right eye of each of these animals was removed before the beginning of the injection series; the left eye was removed shortly after the fifth cortisone injection. The experimental group included eight females and six males. Counts for both males and females analyzed separately showed a statistically significant increase in mitosis numbers after cortisone treatment (three or more times the standard deviation of the difference). For both groups taken together there was an average increase in mitosis count of 24%, which was 3.5 times the standard deviation of the difference. An experiment was performed on eight rats after five days of cortisone administration to test the decline in mitosis numbers following ether anesthesia. The decline was found to be normal. It is

TABLE 2.—*Cortisone and Hypophysectomy*

	No. Animals	Mitosis Counts	
		Before Cortisone (10 Days After Hypophysectomy)	After Cortisone (15 Days After Hypophysectomy)
Experiment	7	112	68
Saline controls	4	80	69

concluded that the increase in mitosis number after cortisone treatment represents a genuine increase in the mitosis rate in the rat's corneal epithelium.

In order to explore the mechanism of this mitotic stimulation, the experiment was repeated on hypophysectomized rats. Hypophysectomized rats were obtained from the Hormone Assay Laboratory on the third postoperative day. On the 10th day after operation the right eyes of all the rats were removed for mitosis counts. Seven animals were then given five daily doses of 5 mg. of cortisone intramuscularly. Four animals received daily saline injections, as controls. All left eyes were removed on the 15th postoperative day. Both the cortisone-treated animals and the controls showed similar declines in mitosis counts (Table 2). It is concluded that the increased mitosis following cortisone treatment in normal rats cannot be produced in the absence of the pituitary gland. Furthermore, the decline in mitosis count in hypophysectomized animals is not due to diminished supply of cortisone, a conclusion already established by the absence of mitotic decline following adrenalectomy.

Normal animals injected daily with 5 mg. cortisone on the first day and with 2.5 mg. for the succeeding four days, were subjected to pinprick wounds of the corneal epithelium. Eyes were removed at one, one and a half, two, and three hours after the injury and compared with an equal number of specimens from a simultaneous control series in which the corneal injuries were produced without preceding cortisone treatment. No differences were found in the healing rate or in the morphology of the healing process between the treated animals and the

controls. It should be remembered that these wounds were epithelial, and the negative results of this experiment in no way contradict the well-established inhibition of healing of connective tissue wounds by cortisone.

8. CORTICOTROPIN

Rats were given daily injections of 5 mg. of corticotropin dissolved in gelatin solution daily for 10 days. The right eye of each animal was removed before the course of injections; the left eye, at the end of the series. Mitosis numbers were normal in both. An ether experiment on seven similarly treated animals showed a normal rate of decline in mitosis numbers. Since it was thought possible that an effect of corticotropin on wound healing might be rapid and transitory, pinprick wounds in rat's corneal epithelium were made three hours after intramuscular injection of corticotropin in aqueous solution. No effect on wound healing was noted.

9. HEPARIN

Solutions of 5 to 10% heparin in isotonic buffer were administered every 5 to 10 minutes for five instillations to one eye each of a group of rats. The control eye received similar instillations of buffer solution only. The animals were killed one-half to one hour after the last instillation. No significant differences were found in the mitosis numbers between the treated and the control eyes.

In order to assay the rate of progress through mitosis under heparin, the following experiment was performed: Ten per cent heparin in isotonic phosphate buffer was instilled into one eye each of five rats, every 10 minutes for 1½ hours. The control eyes received buffer solution only. Half an hour after the beginning of the instillations 0.15 mg. of epinephrine was injected intramuscularly in each animal. Seventy minutes later both eyes were removed. The mitosis counts were equally low in the two eyes.

Ten per cent heparin in isotonic buffer solution was instilled in one eye of each of eight rats every 10 minutes for three times before pinprick wound of the cornea and every 15 minutes after the injury until the animals were killed. The control eyes received instillations of buffer only. Half the animals were killed two hours, the other half three hours, after the injury. Retardation of wound healing was conspicuous in the heparin-treated as compared with the control eyes in both groups. Quantitative estimation of the retardation is difficult, but, roughly, the heparin-treated eyes showed at three hours about the same degree of healing as the control eyes at two hours.

10. COMMENT

Diminution in mitotic activity in the corneal epithelium following hypophysectomy is striking. The counts are only slightly lower than normal 10 days after operation but are severely reduced two weeks after operation. This delay in the onset of the reaction suggests that this effect, like so many other consequences of hypophysectomy, may be indirect. It is not, however, consequent upon diminished activity of thyroid or adrenal, since removal of either of these organs is without effect. It may be that the absence of the growth hormone is responsible for the change, but until fractionation of the various pituitary hormones has proceeded to the point of making separate replacement therapy possible, speculation on the mechanism of this effect would appear idle.

Thyroidectomy and thyroxin administration were both without effect on the phenomena studied. Smelser [4] has reported in similar experiments that mitosis rates were unchanged. However, he found that the healing of large corneal epithelial defects produced by heat injury to the tissue was somewhat slower than normal in animals treated with thyroxin. In previous studies in this series we have repeatedly pointed out that the healing of large corneal abrasions is a much more complicated affair than the healing of pinprick wounds. Moreover, our experiments with thyroxin were maximally acute, while Smelser's were chronic. There is, therefore, no contradiction between our findings and those of Smelser.

Parathyroidectomy, alloxan diabetes, and adrenalectomy were all without effect on the phenomena studied.

The parenteral administration of cortisone caused a definite increase in the mitotic rate in the corneal epithelium and had no effect on the healing of pinprick wounds in the corneal epithelium. The effect of cortisone on mitotic activity has not heretofore been the subject of many studies. Green and Ghadially [5] report that mitotic activity in the mouse's skin is inhibited by cortisone. Bullough [6] induced stress in mice by overcrowding and found diminished mitotic activity in the skin. He found that epinephrine has a powerful antimitosis action on this tissue, both in vivo and in vitro, and that cortisone produced similar results. Steen [7] found no effect of cortisone in doses comparable to those used therapeutically when applied to tissue cultures of chick fibroblasts and chick epithelium. With excessively large doses, mitotic inhibition was produced, but the author attributes these to indirect effects. Roberts [8] found that cortisone delayed the onset of mitotic activity in the liver following partial hepatectomy, but that after regeneration got under way the mitotic rate was normal in spite of continued administration of cortisone. In tissue cultures of rabbit brain, Geiger and Behar [9] report that cortisone increased the survival time of individual neurones, prevented growth of most cells other than neurones, and increased the frequency of mitosis in neurones tenfold to twentyfold. It would appear that the influence of cortisone on cell multiplication varies with tissue, species, and mode of administration.

In regard to wound healing the literature is much less confused. Practically all investigators agree that the healing of connective tissue is delayed by cortisone. Duke-Elder and Ashton [10] were unimpressed by the effect of cortisone on epithelial regeneration in the cornea but found that repair of corneal endothelial defects was retarded. Our experiments confirm those of Duke-Elder and Ashton with respect to corneal epithelial repair.

We were unable to demonstrate any effect by corticotropin on the phenomena studied. This finding is not necessarily in conflict with our experiments with cortisone, since it is doubtful whether even with maximal doses of corticotropin the rat produces as much as 5 mg. of cortisone daily, the latter being the dose which we used in our experiments.

Inhibition of healing of epithelial wounds in the cornea by heparin accords well with numerous reports on the inhibition of cell migration in tissue cultures by this agent.

SUMMARY AND CONCLUSIONS

Hypophysectomy in rats is followed by a diminution in mitotic activity in the corneal epithelium.

MITOTIC AND WOUND-HEALING ACTIVITIES

Parenteral administration of cortisone caused an increase in mitotic rate in the rat's corneal epithelium.

Local administration of heparin delayed the healing of pinprick wounds in the rat's corneal epithelium.

Thyroidectomy, thyroxin administration, parathyroidectomy, adrenalectomy, alloxan diabetes, and corticotropin administration were all without effect on mitotic and wound-healing activities in the rat's corneal epithelium.

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EFFECT OF ACETAZOLEAMIDE (DIAMOX) ON CARBONIC ANHYDRASE ACTIVITY OF ANTERIOR UVEA OF THE RABBIT EYE

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THE DRAMATIC effect of acetazoleamide (Diamox; 2-acetylamino-1,3,4-thiadiazole-5-sulfonamide), a potent carbonic anhydrase inhibitor, in lowering intraocular pressure * has focused attention upon the possible role of the enzyme in the secretory mechanism of the ciliary body and iris. This association is particularly suggestive in view of the report by Wistrand [2] of the presence of carbonic anhydrase activity in the ciliary body and iris of the rabbit eye. It was deemed of fundamental importance, therefore, to determine whether the administration of acetazoleamide affected the carbonic anhydrase activity of the ciliary body and iris.

METHODS

Carbonic anhydrase activity was measured in a Warburg apparatus at 1 to 2 C. according to the method of Krebs and Roughton.[3] The amount of blood in the tissue was determined with the benzidine reaction, according to Ashby and Chan.[4] Known dilutions of venous blood, drawn from the same rabbit from which the tissue in question was taken, were compared with dilutions of the tissue extract.

EXPERIMENTAL SAMPLES

Pigmented adult rabbits, weighing 4 to 6 lb. (1.8 to 2.7 kg.), were used.

Samples of blood (0.027 ml.) were drawn from the ear vein with a calibrated blood dilution pipette, hemolyzed with 0.2 ml. of 0.1 N HCl, and finally diluted to 25.0 ml. with 0.1 M PO_4 buffer, pH 6.95. For the assay of carbonic anhydrase activity of blood, 0.75 ml.† was used. Further serial dilutions were made with distilled water for the benzidine test.

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† This amount was found to be equivalent to the residual blood in the extract prepared from one ciliary body and iris.

A solution of the sodium salt of acetazoleamide ‡ was injected into the ear vein of the rabbit, 30 mg. per kilogram of body weight. The animals were killed by air embolism. In order to facilitate drainage of the blood from the ocular tissues, the animals were held in an upright position and air was injected into the anterior chamber. The eyes were then enucleated and the ciliary body and iris removed together under isotonic saline solution and freed of surrounding tissue and vitreous humor. The blotted tissues from three animals were homogenized in a Potter-Elvehjem homogenizer in 6.0 ml. of 0.1 M phosphate buffer, pH 6.95, at 0 C. A slightly opalescent extract was obtained after centrifugation in an International Refrigerated Centrifuge, PR-1, at 0 C. and at 4,000 rpm for 20 minutes. One milliliter of the extract, equivalent to one ciliary body and iris, was pipetted into the main compartment of a Warburg flask and diluted to 2.0 ml. with phosphate buffer. The side-arm contained 1.0 ml. of 0.154 M $NaHCO_3$. The flask and its contents were equilibrated in the Warburg bath without shaking § for 30 minutes. The manometers were adjusted for the 0-minute reading and the side-arm contents rapidly tipped into the main compartment. Manometer readings were recorded at 10-second intervals up to 1 minute. The identity of the conditions (pH and concentration of buffer) in the flasks of a single experiment was checked by measuring the final value (after 10 minutes) of CO_2 liberation. In all experiments, controls in the absence of tissue extract were also run, and the values obtained were subtracted from those with the experimental samples.

For the estimation of the content of residual blood in the tissue, 0.1 ml. of the extract was serially diluted 100, 200, and 400 times with distilled water.

Determination of Residual Blood in Extract by the Benzidine Test*

Dilution		Blood Found in Diluted Extract, μl/Ml.	Blood Calc'd. in Original Extract, μl/Ml.
Extract †	Blood ‡		
1:100	$1:1.25 \times 10^5$	0.008	0.8
1:200	$1:2.37 \times 10^5$	0.004	0.8

* Venous blood of the animal used as a standard.
† Extract: 1.0 ml. of the extract equivalent to one ciliary body and iris diluted as indicated.
‡ Blood: 0.027 ml. of venous blood hemolyzed and diluted to 25 ml.; final dilutions as indicated.

RESULTS

The accompanying Table gives the amount of residual blood in extracts prepared from the ciliary body and iris tissues as compared with venous blood from the same animal. After the first three experiments gave consistent values of 0.8 μl of blood remaining in 1.0 ml. of extract, corresponding to one ciliary body and iris tissue, this value was accepted as representative of the residual blood with the described technique.

It is obvious from Figure 1 that the carbonic anhydrase activity of the extract is almost wholly derived from the tissue itself and that only a negligible amount is contributed by the residual blood.‖ Except for the slight hump at 10 seconds, the curve is linear for at least 60 seconds. For quantitative determination, however, in accordance with Krebs and Roughton,[3] the quantity of CO_2 developed during the first 30 seconds is used as the basis for comparative evaluation. By plotting the 30-second values as percent inhibition of carbonic anhydrase activity, the curve in Figure 2 is obtained. This shows clearly that as early as 15 minutes after the

‡ Diamox was supplied by Dr. James D. Gallagher, Lederle Laboratories Division, American Cyanamid Company, Pearl River, N. Y.

§ Leiner [5] showed that carbonic anhydrase may be denatured in very dilute aqueous solution on shaking.

‖ This relationship justifies the use of the simple experimental technique described and suggests that the more involved and less physiologic technique of perfusion is unnecessary.

intravenous administration of acetazoleamide 75% inhibition of the enzyme occurs. The maximum inhibitor is reached in 30 minutes. The rate of recovery of the activity is much slower, so that even 17 hours later only 60% of the original activity is restored.

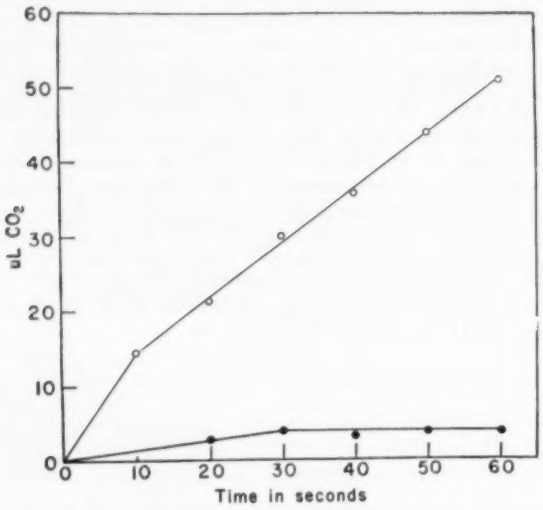

Fig. 1.—Carbonic anhydrase activity of residual blood in extract from ciliary body and iris. Measured in Warburg apparatus at 1 to 2 C. Main compartment: 1.0 ml. of extract or 0.75 ml. of blood (1 : 925) made up to 2.0 ml. with 0.1 M PO_4 buffer, pH 6.95. Side-arm, 1.0 ml. of 0.154 M $NaHCO_3$. Gas atmosphere, air.

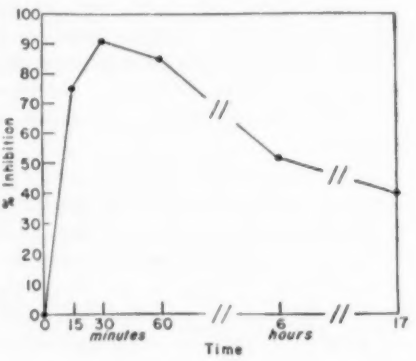

Fig. 2.—Effect of acetazoleamide on carbonic anhydrase activity of ciliary body and iris. Ordinate: Microliters of CO_2 generated in 30 seconds in terms of percent inhibition. Abscissa: Time after intravenous administration of acetazoleamide that the animal was killed. Same experimental conditions as in Figure 1.

COMMENT

The introduction of acetazoleamide therapy into ophthalmology for the treatment of glaucoma and the present discovery of its inhibitory properties on the carbonic anhydrase activity of the ciliary body and iris suggest the involvement of this enzyme in the mechanism of the secretion of bicarbonate ions into the posterior chamber.

Friedenwald [6] has postulated that the bicarbonate secreted into the posterior aqueous is formed in the ciliary epithelium by the reaction of CO_2 with hydroxyl ions, according to the equation,

$$OH^- + CO_2 \rightarrow HCO_3^- \qquad (1)$$

The hydroxyl ions are assumed to be derived from the oxidation of reduced cytochrome oxidase by molecular oxygen, forming reduced oxygen (O^-), which, in turn, reacts with H_2O to generate $2OH.^-$ The higher pH of the posterior aqueous [7] as compared with that of blood plasma has been offered as support for this assumption.

It is generally held that bicarbonate ion is secreted by the ciliary body into the posterior aqueous. The postulate that the bicarbonate ion is continuously formed by the neutralization of CO_2 by OH^- generated by the transfer of electrons from reduced cytochrome oxidase by molecular oxygen, however, may be questioned on two grounds.

A. In aqueous solutions CO_2 engages in the following reactions [8]:

$$CO_2 + H_2O \rightleftarrows H_2CO_3 \qquad (2)$$

and in Reaction 1, previously given.

Below pH 7.5 the OH^- is so small that the rate of Reaction 1 is negligible as compared with that of Reaction 2. Above pH 11, on the contrary. Reaction 1 predominates, while between pH 8 and pH 10 the rates of both reactions are significant. Reaction 1 may also be considered a catalysis of Reaction 2 by hydroxyl ions. In view of the pH of blood (7.4) and that of the aqueous humor (anterior, 7.60; posterior, 7.57),[7] the contribution of Reaction 1 in the formation of bicarbonate ion by the ciliary body is probably very slight.

B. Recently Ball [9] has presented evidence indicating that reduced cytochrome oxidase reacts with molecular oxygen in a manner similar to that of hemoglobin and myoglobin. In a step-wise fashion, then, the Fe^{++} of the enzyme is oxidized to Fe^{+++} and the O_2 is reduced to H_2O_2. The latter then reacts with H^+ to form H_2O. This mechanism does not postulate the theoretical formation of OH^- from the oxidation of reduced cytochrome oxidase.

In view of the foregoing discussion and the present findings, it is proposed that a more probable mechanism for the formation of bicarbonate ions by the ciliary body is the hydration of CO_2 mediated by the enzyme carbonic anhydrase.

Experiments designed to test this possible mechanism are now in progress.

SUMMARY

Carbonic anhydrase activity of the ciliary body and iris of the rabbit was determined on extracts in a Warburg apparatus. The residual blood in the tissue contributed only a negligible amount to the over-all enzymatic activity. The intravenous administration of acetazoleamide (Diamox), 30 mg. per kilogram, caused a 75% inhibition of the carbonic anhydrase activity in 15 minutes and a maximum of 93% in 30 minutes. After 17 hours only 60% of the original activity was restored. It is suggested that carbonic anhydrase in the anterior uvea of the rabbit may be directly involved in the formation of bicarbonate ions found in the aqueous humor.

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A NEW MAGNETIC ORBITAL IMPLANT

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INCREASING dissatisfaction with the results obtained after enucleation and the insertion of a glass or plastic sphere implant led to efforts to improve these results by changing the character of the implant and making associated changes in the artificial eye. This work was possible only because our Plastic Artificial Eye and Restorations Clinic had the facilities for such work, and the personnel members had the necessary knowledge and experience not only to follow suggestions closely but to suggest valuable changes themselves.

The totally buried type of implant offers the best results because of the absence of discharge and the slight tendency to dehiscence and extrusion. During 1948 eight different types of buried implants were developed and inserted clinically. The final model developed was similar in size and shape to that to be described in this paper. With this, there was excellent mobility of the implant itself and no tendency to extrusion, and the space left after enucleation was well filled. The transmission of the motion of the implant to the artificial eye was still quite imperfect, and, since the implant did not support the weight of the artificial eye, this weight was still borne by the lower lid, with consequent drooping of the lid.

It became evident that to get satisfactory mobility and support of the artificial eye some form of integration would be necessary. Mechanical integration was not possible with a totally buried implant; therefore, the concept was evolved of employing a magnetic field set up between a magnet in the implant and one in the artificial eye which could effect this integration through the interposed Tenon's capsule and conjunctiva. Linkage of this type has been termed "semi-integration" (Hughes [1]).

The so-called bipolar magnet, in which both poles are in the presenting end or face, offers advantages over the monopolar type. The magnetic field set up by the bipolar type is closed and more efficient for the same size magnet. Orientation of

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the artificial eye is automatic. There is one position in which these poles will attract each other maximally and, the implant position being fixed as regards rotation, the artificial eye will immediately rotate to its proper alignment.

The implant which is now used (Fig. 1) is 17 mm. in its greatest horizontal diameter, tapering slightly to 15 mm. at the anterior surface, which is flat. The posterior surface is a segment of a sphere, highly polished, to offer little resistance

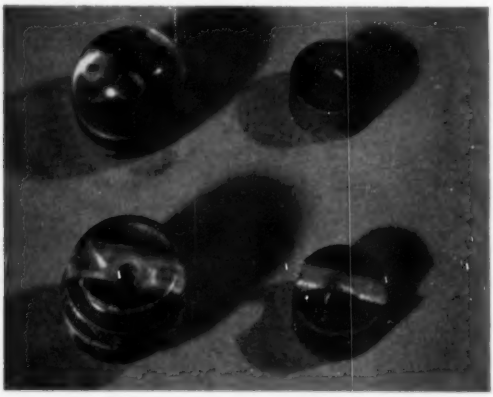

Fig. 1.—Anterior and posterior views of the implant and of the magnet enclosed within it.

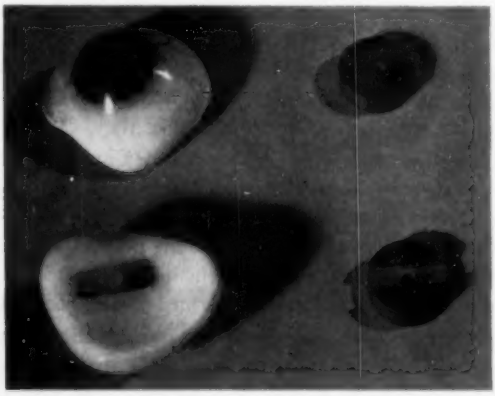

Fig. 2.—Anterior and posterior views of the artificial eye and of the magnet enclosed within it.

to movement within the tissues of the orbit. The body of this implant is fabricated in three anteroposterior lengths, 16, 14.5, and 13 mm. As a rule, in primary insertions, at the time of enucleation, the 16-mm. size is inserted. The smaller sizes are usually used in secondary or late insertions. The magnets used are of the Sintered Alnico II type, that in the implant (Fig. 1) measuring 13 mm. horizontally and 6.5 mm. anteroposteriorly and weighing 4.8 gm., while that in the artificial eye (Fig. 2) is 13 by 2.5 mm. and weighs 1.7 gm.

The magnetic pull of these magnets has always been great enough to allow a margin for reduction of pull to reduce pressure on the interposed tissue when necessary. The thickness of plastic over the magnet can be varied or the magnet itself reduced in thickness to reduce the pull, and this can be changed in the artificial eye at any time. This magnetic pull has shown no appreciable change in any of our cases during the period of observation, and the use of these magnets in industry for many years has given no indication that such change will occur. Shock, vibration, and temperature changes within the tolerance of the human body will cause no change in this magnetic field. Metallic shell fragments in the orbit have not had any effect on the magnetic field, since the magnet is thoroughly insulated by plastic. The presence of this implant in the orbit does not have any effect upon electroencephalographic or electrocardiographic tracings. It has been stated by Troutman [2] that the presence of a magnet does not predispose to dehiscence of the conjunctiva.

Near the anterior end of the implant body a band of tantalum mesh 3 mm. wide is attached. This location makes possible an attachment of the rectus muscles anterior to the center of rotation of the implant-artificial eye combination, as is considered necessary by Culler.[3] This mesh is Ethicon 50 by 50 tantalum mesh woven of wire of 0.003 in. diameter, applied in a single layer. To enable one to pass a needle through such mesh easily and to minimize damage to it by the needle and suture, a shallow groove is machined in the plastic beneath the mesh. It is essential that this mesh be applied so as to preserve the correct interval between woven wires. Reports by Stone [5] show that when mesh is applied with the wires crowded too close together, the fibrous tissue will not grow into the mesh.

The body of this implant is composed of thoroughly polymerized methyl methacrylate, as a single transparent unit, no insert sections or cements being used. The magnets are incorporated into both the implant and the artificial eye at the time of molding.

The insertions which we are now reporting have been performed by 12 different operators, including both senior and junior residents on our service. The technique used by us is as follows:

General anesthesia is used. Enucleation is performed in the usual way; the rectus muscles are grasped and retained in mosquito clamps. The use of a tonsil snare for the actual enucleation and cutting of the optic nerve produces a practically bloodless field. Double-armed tantalum braided sutures, 00000, are placed in the implant before its insertion, passing through the mesh at four points—at each end of the groove in the magnet and midway between these points. The implant with preplaced sutures is placed in the cavity of Tenon's capsule with the groove of the magnet in a horizontal position. The sutures are then passed through the four rectus muscles and through Tenon's capsule, and are drawn up and tied as mattress sutures on the outside. These sutures should be drawn up snugly but not tightly, should have three knots, and should be cut off very short. The excess of Tenon's capsule is now brought over the front of the implant and closed with interrupted chromic 0000 absorbable (gut) surgical sutures. The conjunctiva is closed by a running, untied 0000 nonabsorbable (silk) suture.

In secondary insertions the muscles are not separated and attached separately. The sutures are passed through Tenon's capsule at four points, corresponding as nearly as possible to the location of the rectus muscles, and are tied as mattress sutures.

The operation, including the induction of general anesthesia, has required an average of 1 hour 15 minutes. For postoperative care, no pressure dressing is used. None is needed if there is proper hemostasis. Use of antibiotics is begun, when possible, the day before enucleation and is continued for five days. Preference is given to penicillin in a dosage of 300,000 units twice a day.

Certain points in this technique need emphasis:

1. In all handling of the implant care must be taken to avoid trauma to the mesh.

2. Braided 00000 tantalum sutures are used to get permanent attachment of muscle to the tantalum mesh. It has been shown that slipping is many times more frequent after the use of silk, which also acts as a foreign body. Catgut does not last long enough, and nylon stretches (Cutler [4]; Stone [5]). Thus, tantalum remains the only satisfactory suture material for our purpose.

3. The implant is inserted with the groove in the magnet placed horizontally because the maximum magnetic force is across the poles and in this position the artificial eye is best supported and its weight taken off the lower lid.

4. The suture line in Tenon's capsule and that in the conjunctiva should be so placed that they do not overlie each other. This minimizes danger of dehiscence.

5. Exact closure of Tenon's capsule is very important, as conjunctiva alone over the plastic surface is often nonviable.

6. The technique described in secondary insertions has been used because results have been as good as those after muscle separation and attachment, a procedure which is always very difficult and usually results in damage to muscles because of scar tissue in the orbit.

The artificial eye is not inserted until eight weeks after operation, to allow the subsidence of all edema and swelling. Culler [3] has said that the conjunctiva will remain thickened unless subjected to pressure. This has been found to be true, and for this reason a conformer with attached magnet covered with wax is inserted several days before fitting of the artificial eye. Best results are attained when the surgeon gives consideration to the needs of the prosthetic technician in his postoperative fitting. Such items as selection of the proper size of implant to avoid proptosis and the preservation of conjunctiva to form sulci without tension are important.

RESULTS OF USE

The first insertion of this implant was on Nov. 2, 1949. Since that time it has been used in 117 cases, in 81 of which the insertions were primary and in 36 secondary. The secondary intervals varied from slightly over 1 year to more than 20 years. These enucleations were performed for the usual variety of reasons, trauma being the cause in 38 cases. It is very difficult, in a series of cases of such diverse nature, to express the actual mobility in figures. It is extremely difficult to judge the secondary cases, with their complicating factors, such as deficiencies in musculature and scar formation within the orbit, by the same criteria used for primary insertions. However, the following tabulation expresses our estimate of the mobility attained:

	Less than 80%	80-100%
Primary	10	71
Secondary	23	13

Deficiency in mobility, when present, is most frequently in one direction only and can often be rectified or improved by changes in the artificial eye.

Other Factors.—In examination of these 117 patients, the following results were found:

Extrusions (two cases): One patient developed infection about the implant one month after insertion and the implant was removed. This insertion was secondary after the removal of another type of implant, inserted elsewhere, and the infection is believed to have been due to the insertion of our implant before the infection in the orbit had entirely subsided.

The second patient developed infection about the implant after a dehiscence occurring one year after insertion. The reason for this dehiscence was not determined. These two cases may be regarded as failures, since no implant was reinserted.

Dehiscences (six cases): One dehiscence was complete very shortly after insertion, but the patient has not had discharge or other trouble. The patient has very good function, after four years. Dehiscence is thought to have been due to imperfect closure of Tenon's capsule and conjunctiva.

A second patient had dehiscence beginning several years after insertion and developing slowly after progressive thinning of the tissue over the implant. This insertion was the first done in 1949 and the dehiscence is believed to have been due to excessive magnetic pull and resultant pressure necrosis of the conjunctiva. The size and power of the magnets have since been reduced, and no other pressure necrosis has occurred.

The other four dehiscences have been small. Two have been secondarily closed; two others have not. Very moderate discharge occurred in one of the latter but cleared quickly. There has been no dehiscence in the past three years.

Other Findings: There has been no discharge, abnormality of the conjunctiva, or granulation tissue in any case of nondehiscence.

No cellulitis or allergic reaction has occurred.

No tilting or rotation of the implant or proptosis has occurred.

Several patients showed sinking in of the upper lid, due not to dropping of the artificial eye but to postenucleation atrophy of orbital tissues.

The tantalum mesh did not become exposed in any case, nor did it break down in any way, the condition being proved by x-ray examination. Thirty-eight patients have been so examined within the past month.

SUMMARY AND CONCLUSIONS

A detailed account of the development, fabrication, and technique of insertion of a new magnetic orbital implant is presented.

The results attained by the use of this implant and its associated artificial eye in 117 patients are given.

The complications and failures are discussed.

This magnetic implant seems to have the following advantages:

1. Simplicity of operative procedure.

2. Excellent mobility. The mobility of the artificial eye is that of the implant and can be, and often is, that of the normal eye.

3. Absence of cellulitis or allergic reactions.

4. A minimum of discharge, dehiscence, and extrusions.

5. Maintenance of correct position of the artificial eye. The magnets used being bipolar, after they are once oriented properly, the artificial eye always returns to the correct position.

6. Support of the artificial eye by magnets so that it makes no pressure on the lower lid.

7. Absence of tilting or rotation of the implant or of proptosis.

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INTRAOCULAR PENETRATION OF LOCAL HYDROCORTISONE AND CORTISONE

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THE EXPERIMENTS to be reported in this paper were undertaken for the purpose of determining steroid levels in the aqueous humor following subconjunctival injections or topical applications of cortisone acetate or hydrocortisone acetate.*

The results of such studies were reported earlier from this laboratory † and by others.‡ The results were similar, but because of certain difficulties and inadequacies of the methods employed, discussed in a later paper from this laboratory,[5] it was deemed of importance to reinvestigate this problem, using certain essential modifications in the analytical methods.

METHODS

Adult rabbits, approximately 4 lb. (1.8 kg.) in weight, were used. The aqueous humor was removed with a 26-gauge needle and tuberculin syringe by means of an oblique corneal puncture. The eyes were previously anesthetized by the instillation of two drops of 0.5% tetracaine hydrochloride and were thoroughly flushed with isotonic saline before the aqueous humor specimens were removed for analysis with the Porter-Silber test.[4]

The aqueous humor was added directly to chloroform and was extracted four times at a ratio of 1 vol. of aqueous humor to 5 vol. of chloroform. The ratio of aqueous humor to chloroform was found to be adequate to prevent the formation of emulsions, which might prevent the complete extraction of any steroids present. This was noted in an earlier report from this laboratory (Green and Leopold [6]).

The chloroform extracts were evaporated to dryness with the aid of a vacuum pump and a water bath at approximately 45 C. This evaporation technique is of great importance in these studies because chloroform extracts of rabbit aqueous humor contain a highly volatile fraction which gives a positive test for steroids by the Porter-Silber test, as previously reported.[5] However, none of the six "active" adrenocortical steroids, or any other steroid so far tested, will evaporate under these conditions.[5]

After evaporation, the aqueous humor residues were taken up in absolute methanol and tested for their response to the Porter-Silber test. Of the known adrenocortical steroids, the Porter-Silber test is positive for cortisone, hydrocortisone, desoxycortisone (Compound S), and two or three inactive adrenosteroids.

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* Merck & Company, Inc., and Pfizer Laboratories supplied the cortisone and hydrocortisone.

† References 1, 2, and 3.

‡ References 8 and 9.

The Porter-Silber test was modified in volumes of reagents used, as follows: absolute methanol, 0.2 ml.; dilute sulfuric acid or phenylhydrazine in dilute sulfuric acid, 1.27 ml. Optical densities were measured at 410 mμ with the Beckman spectrophotometer, model DU, using 1 ml. microcells (light path = 1 cm.).

A white precipitate was formed in the extracts of aqueous humor from NaOH-burned eyes. This was readily removed by washing the chloroform extracts once with 1 vol. of glass-distilled water to 5 vol. of chloroform. This washing procedure does not remove cortisone when it is present in quantities as low as 1 γ.

The effect of this washing procedure on the levels of Porter-Silber-positive material recovered from the aqueous humor of normal and of NaOH-burned eyes is shown in Table 1.

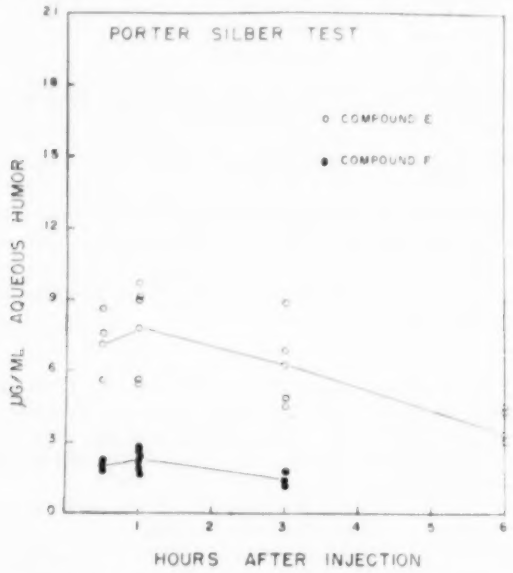

TABLE 1.—*Effect of Washing on Levels of Porter-Silber-Positive Substances in Chloroform Extracts of Normal and Secondary* Aqueous Humor†*

Normal		Secondary *	
Unwashed	Washed ‡	Unwashed	Washed ‡
0.0 γ/Ml.	0.0 γ/Ml.	3.8 γ/Ml.	1.7 γ/Ml.
0.0 γ/Ml.	0.0 γ/Ml.	1.3 γ/Ml.	0.7 γ/Ml
0.9 γ/Ml.	0.5 γ/Ml.	2.2 γ/Ml.	0.5 γ/Ml

* NaOH-Burned eyes.
† Quantities expressed in terms of hydrocortisone per milliliter of aqueous humor.
‡ See text.

RESULTS

1. *Subconjunctival Injections in Normal Eyes.*—The original plan of research was to inject the steroids subconjunctivally at the same concentrations as those used clinically and to determine the times for penetration into the aqueous humor and disappearance from the aqueous humor. The first tests with a subconjunctival injection of 12.5 mg. (the clinical dose) of cortisone acetate were negative, and the dose was then increased to 50 mg. It was necessary to pool the aqueous humor from four eyes in order to obtain measurable quantities of steroids. The results are shown in the accompanying Chart.

(*a*) Cortisone Acetate: Detectable levels of Porter-Silber-positive substance were found one-half hour after the injection. The levels had begun to decrease by three hours after the injection.

(*b*) Hydrocortisone Acetate: Traces of Porter-Silber-positive material were found one-half hour after the injection. The levels appeared to fall by three hours after the injection.

2. *Subconjunctival Injections in Abraded Eyes.*—The eyes were abraded by scratching the cornea with the back of a scalpel. The eyes were injected at various time intervals following abrasion. The aqueous humor was removed one hour after the injection.

TABLE 2.—*Levels of Porter-Silber-Positive Materials in Aqueous Humor of Normal and of Abraded Eyes One Hour After Subconjunctival Injection of 50 Mg. of Cortisone Acetate* *

Normal Eye No Steroid	Normal Eye Subconj. Inj.	Abraded Eye Subconj. Inj.
— †	5.5	9.2 ‡
—	5.6	13.6 ‡
—	9.0	5.6 §
—	10.3	8.1 §
—	9.7	9.4 §
..	...	10.4 ‖
..	...	6.5 ‖

* Micrograms of steroid per milliliter of aqueous humor in terms of hydrocortisone.
† — indicates original optical density less than 0.05. See text.
‡ Abraded just preceding steroid injection.
§ Abraded two hours preceding steroid injection.
‖ Abraded 27 hours preceding steroid injection.

TABLE 3.—*Levels of Porter-Silber-Positive Material in Aqueous Humor of Normal and NaOH-Burned Eyes One Hour After Subconjunctival Injection of 50 Mg. of Cortisone Acetate or Hydrocortisone Acetate*

No Steroid		Cortisone Acetate		Hydrocortisone Acetate	
Normal	Burned	Normal	Burned	Normal	Burned
—*	2.4 †	5.5	15.6	—	—
—	—	5.6	17.9	—	2.4 †
—	—	...	....	..	...

* Original optical density less than 0.05.
† Value calculated from an original optical density between 0.05 and 0.10. See text.

(*a*) Cortisone Acetate: There was no difference in the penetration of cortisone in the normal and in the abraded eyes. The results are summarized in Table 2.

3. *Subconjunctival Injections in Normal and in NaOH-Burned Eyes.*—The eyes were burned by the application of one drop of 1 N sodium hydroxide for 15 minutes, followed by thorough flushing with isotonic saline. The subconjunctival injections were then made, and the aqueous humor was removed one hour after injection.

(*a*) Cortisone Acetate: There was approximately a threefold increase in the penetration of cortisone acetate into the burned eyes.

(*b*) Hydrocortisone Acetate: The optical densities were too low for the accurate calculation of the quantities of steroids present.

The results are summarized in Table 3.

4. *Topical Applications in Normal and in NaOH-Burned Eyes.*—One drop of 2.5% suspension of the steroid was made every 15 minutes for one hour. Fifteen minutes after the last drop the eyes were proptosed and thoroughly flushed with isotonic saline and the aqueous humor removed.

(*a*) Cortisone Acetate: There was, again, an approximately threefold increase in the penetration of cortisone acetate in the burned eye, as compared with the normal eye.

(*b*) Hydrocortisone Acetate: There was a slight increase in the penetration of hydrocortisone (Compound F) in the burned eye.

The results are summarized in Table 4.

COMMENT

These data indicate that locally applied cortisone acetate penetrates the normal and the sodium-hydroxide-burned eye better than does hydrocortisone acetate. However, it is possible that the hydrocortisone may be altered more rapidly after its pene-

TABLE 4.—*Levels of Porter-Silber-Positive Material in the Aqueous Humor of Normal and NaOH-Burned Eyes After Drops of Cortisone Acetate or Hydrocortisone Acetate at Fifteen-Minute Intervals**

No Steroid		Cortisone Acetate		Hydrocortisone Acetate	
Normal	Burned	Normal	Burned	Normal	Burned
—†	—	8.4	21.9	—	3.3‡
—	—	8.7	21.5	2.3‡	5.2‡
—	2.0‡	5.3‡	13.3	2.1‡	4.1

* Micrograms of steroid/ml. aqueous humor in terms of hydrocortisone.
† Original optical density less than 0.05.
‡ Original optical density between 0.05 and 0.10. See text.

tration than cortisone in such a manner as to be no longer detectable by this technique. Such a change, however, would have to take place very rapidly.

The data also demonstrate the need for more sensitive analytical methods.

With the exception of 1 case out of 13, the optical densities of the pooled normal aqueous humor fell below 0.05 and were therefore not calculated. A consideration of optical densities is important because the optical density should fall within a certain "working range." This range is about 0.100 to 0.700.§ In this paper original optical densities falling below 0.25 were not calculated. Original optical densities falling between 0.05 and 0.10 have been marked with an asterisk.

It has been noted clinically that local hydrocortisone is more efficacious than cortisone in the therapy of vernal conjunctivitis (McDonald, Leopold, Vogel, and Mulberger.[11] In intraocular inflammations the difference in anti-inflammatory action of local cortisone and that of hydrocortisone was not so apparent. Similarly in controlled induced experimental corneal vascularization local cortisone appeared to be superior to local hydrocortisone in preventing vascularization.[11] Perhaps this difference in effectiveness could be explained by the greater intraocular penetration of the less anti-inflammatory compound, cortisone, as demonstrated by these studies. It is conceivable that the action of local hydrocortisone in intraocular conditions could be enhanced if its penetration were increased.

§ References 5 and 6.

SUMMARY

The appearance of Porter-Silber-positive material in the aqueous humor of rabbits was detected following the subconjunctival injection or topical application of cortisone acetate or hydrocortisone acetate in normal or sodium-hydroxide-burned eyes. In order to do this, however, it was necessary to use abnormally large quantities of the steroids and to pool the aqueous humor from several eyes.

Cortisone penetrated the anterior chamber in higher levels than did hydrocortisone. Removal of the corneal epithelial barrier-induced inflammation increased the penetration of both agents.

The need for more sensitive methods in the detection of steroids in the aqueous humor is stressed.

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OCULAR PENETRATION OF PROCAINE FOLLOWING SUBCONJUNCTIVAL INJECTION

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THIS REPORT concerns one phase of a long-range investigation which has been directed toward development of more effective local anesthetic drugs and improved methods of their administration in ophthalmologic practice. In this particular study it has been our purpose to determine factors influencing the ocular penetration and distribution of procaine following subconjunctival injection. By "subconjunctival" we refer to the issue which is under the epithelium of the bulbar conjunctiva but is external to Tenon's capsule. The distribution of anesthetic drugs following subcapsular injections will be investigated later.

Subconjunctival injections of procaine hydrochloride commonly are made if manipulation of the iris is to be required during ocular surgery; however, a review of the literature reveals no unanimity of opinion regarding the efficacy of such injections. Many surgeons advocate this method of anesthesia, whereas others feel that retrobulbar injection is superior for such operative procedures as iridectomy. One per cent procaine hydrochloride in aqueous solution seems the most commonly used preparation for subconjunctival injection, but we have not found its anesthetic effects on the iris to be consistently good. It has seemed to us that a laboratory study of penetration of procaine from the subconjunctival tissues into the anterior segment might resolve this clinically important problem. We have found no data concerning the distribution of local anesthetics into the anterior segment when they have been administered by this technique. Furthermore, the effects of adding vasoconstrictor drugs and hyaluronidase on the penetration of these drugs into the eye have not been determined. Either or both are used commonly in ophthalmic surgery.

The time-honored method of determining the penetration of drugs into the anterior segment has been by quantitative analyses of the aqueous humor at various time intervals after administration of the test drug; however, in previous studies[1] we have observed that the quantity of a given drug in the aqueous humor does not necessarily reflect its concentration in the iris. This is undersandable because the aqueous is not a stagnant pool, and the iris has an active vascular system. In addition to a study of the penetration of procaine into the iris and aqueous, it seemed important to determine its spread into the cornea.

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Albino rabbits weighing between 4 and 5 lb. (1.8 and 2.3, kg.) were anesthetized with sodium pentobarbital injected intravenously. The concentrations of procaine in the cornea, iris, and aqueous were determined at various time intervals after subconjunctival injection of 0.5 cc. of aqueous solutions of 1% procaine hydrochloride. The injections were made under the epithelium about 1 mm. behind the limbus on the temporal side, but the solution rapidly spread around the cornea. Tissue analysis were made at 5-, 10-, and 20-minute intervals after the injections by the techniques [1] which have been described in our previous publications. Results in the eyes of living animals are summarized in Table 1.

There were several noteworthy findings. First, a much higher concentration of procaine was present in the iris than in the aqueous humor. This confirmed our previous observation that the concentration of a drug in the aqueous does not reflect accurately its penetration into the iris. This is important, because frequently conclusions regarding ocular penetration of various drugs, notably the antibiotics, have been based solely on analyses of the intraocular fluids.

A second fact of possible clinical importance is that nearly maximal concentrations of procaine in the cornea and iris often were not reached until 10 minutes after

TABLE 1.—*Average Concentration (Milligrams per 100 cc.) of Procaine in Ocular Tissues Following Subconjunctival Injection of 1.0% Solution in Living Rabbits* *

Time, Min.	Cornea	Iris	Aqueous
5	24.79	6.21	0.78
10	31.98	5.68	2.11
20	32.62	7.56	3.70

* 51 determinations.

injection. These levels were sometimes twice as high as those at 5 minutes. It is probable that penetration through the limbus and sclera in the human eye is even slower than in the rabbit. This would indicate that if the surgeon is depending on anesthesia from subconjunctival injection, he should allow adequate time for the drug to spread into the eye. The sensory innervation of the iris is entirely by the ciliary nerves, so that anesthesia of the sclera and limbic nerve plexuses at the site of injection should not affect the iris sensitivity.

Although there have been numerous reports of penetration of various drugs from the subjunctival tissues into the anterior segment, the mechanisms have not been determined with certainty. The role of the limbic vascular plexus in regard to the movement of water into and out of the corneal stroma has been disputed. There is also a possibility that the anterior ciliary circulation might facilitate the passage of drugs from the conjunctival tissues directly into the iris. If this were so, selection of the site of subconjunctival injection might be important. Considering these possibilities, it seemed desirable to determine the ocular penetration of procaine into the eyes of freshly killed animals, and thereby to evaluate circulatory factors.

Under pentobarbital sodium anesthesia, albino rabbits were killed by clamping the aorta in the chest in order to be certain of immediate cessation of the circulation. Subconjunctival injections of procaine then were made. Tissue analyses were made at 5-, 10-, and 20-minute intervals. Results are shown in Table 2.

Concentrations in the anterior segment gradually reached higher levels than in the eyes of living animals. These findings demonstrate that the limbic plexus of vessels must play a relatively small role in the passage of this particular drug into the intraocular structures. They also demonstrate that the higher concentration of procaine in the iris than in the aqueous cannot be due entirely to circulatory factors.

In general surgery it is common practice to add epinephrine or other vasoconstrictor drugs to solutions of procaine. Epinephrine, by delaying the passage of procaine into the general circulation, prolongs the local anesthesia and reduces the incidence of undesirable systemic effects. It also minimizes bleeding. There have been no reports concerning the effects of epinephrine on the ocular penetration of procaine or on its efficacy for iris anesthesia. These effects might be considerable. Epinephrine has been found to enhance the intraocular effectiveness of subconjunctival injections of penicillin.[2] In another group of experiments, therefore, 1% procaine hydrochloride with 1:5,000 epinephrine hydrochloride was injected subconjunctivally in the eyes of living rabbits. The results are summarized in Table 3. Concentrations of the anesthetic reached significantly higher levels in the iris and cornea when epinephrine was added. The differences were not appreciable in 5 minutes but were quite marked in 20 minutes, suggesting that the beneficial effect of epinephrine probably was due to the confinement of a high concentration of procaine in the limbic area.

TABLE 2.—*Average Concentration (Milligrams per 100 cc.) of Procaine in Ocular Tissues Following Subconjunctival Injection of 1.0% Solution in Freshly Killed Rabbits* *

Time, Min.	Cornea	Iris	Aqueous
5	13.69	10.52	0.87
10	16.79	17.16	2.90
20	41.69	14.13	6.75

* 53 determinations.

TABLE 3.—*Average Concentration (Milligrams per 100 cc.) of Procaine in Ocular Tissues Following Subconjunctival Injection of 1.0% Solution with 1:5,000 Epinephrine Hydrochloride in Living Rabbits* *

Time, Min.	Cornea	Iris	Aqueous
5	20.69	4.88	1.05
10	35.75	12.62	2.66
20	41.69	16.90	4.68

* 49 determinations.

In 1940, Kirby and his associates [3] reported that hyaluronidase when added to solutions of procaine hydrochloride shortened the time of onset of anesthesia of the skin following subcutaneous injections; also, the area of skin anesthetized per unit of injected solution was increased appreciably. They logically postulated that hyaluronidase facilitated the spread of the anesthetic solution in the subcutaneous tissues. Their observations, based entirely on the reaction of the patient to stimulation of the skin, have been substantiated by other observers. Atkinson [4] apparently was the first ophthalmic surgeon to report the use of hyaluronidase. He found that it accelerated the onset of orbicularis akinesia and increased the effectiveness of

retrobulbar injections of procaine and epinephrine. It has been suggested that hyaluronidase might increase the ocular penetration of drugs injected subconjunctively; therefore, it seemed desirable to conduct experiments in which hyaluronidase was added to the procaine solution. Six turbidity-reducing units of hyaluronidase was added to each cubic centimeter of 1% procaine hydrochloride. Tissue analyses were made at 5-, 10-, and 20-minute intervals. Results are summarized in Table 4. The concentrations of procaine in the tissues were equal to or lower than were found at various time intervals after injections of procaine hydrochloride alone. These experiments provide evidence that hyaluronidase in commonly used concentrations does not enhance the ocular penetration of procaine injected subconjunctivally; however, it may have other advantages, such as increasing the area of conjunctival anesthesia and reducing edema from the injection.

COMMENT

The minimal effective concentration of procaine which will block small sensory nerves and nerve endings comparable to those in the iris has not been determined. There are factors of time and anatomy as well as concentration. The sensory nerves

TABLE 4.—*Average Concentration (Milligrams per 100 cc.) of Procaine in Ocular Tissues Following Subconjunctival Injection of 1.0% Solution with 6 T.U. per Cubic Centimeter of Hyaluronidase in Living Rabbits* *

Time, Min.	Cornea	Iris	Aqueous
5	23.73	4.83	0.81
10	21.25	6.17	1.25
20	27.71	3.73	4.13

* 47 determinations.

of the iris do not seem to have either heavy myelinization or thick connective tissue sheaths; consequently, they would be susceptible to blocking by lower concentrations of procaine than would be required to block motor nerves. Concentrations of procaine of at least 35 mg. per 100 cc. seem required to alter conduction in the isolated sciatic nerve of the frog.[5] Our previous studies indicate that lower concentrations may induce some blocking of sensation in the corneal epithelium.[6] It is probable, however, that even the maximal concentrations of procaine which we have found in the iris of rabbits must be below, or barely in, the range of the minimal effective anesthetic levels. It is doubtful whether a greater penetration would occur in the human eye. This probably explains the inconsistent anesthesia that we have observed in the human iris following subconjunctival injections of 1% procaine. Certainly, these data, which cast doubt on the efficacy of subconjunctival injections of this concentration of procaine, emphasize the need for further investigation with stronger concentrations, and particularly with more potent agents, such as benoxinate (Dorsacaine). Preliminary studies of subconjunctival injections of benoxinate reveal that if it is made isotonic with isotonic saline it is well tolerated by the subconjunctival tissues. Considerable importance must be attached to the addition of epinephrine or some other vasoconstrictor drug and to the allowing of adequate time for intraocular penetration of the injected anesthetic. These steps may mean the difference between adequate and inadequate iris anesthesia.

SUMMARY

The distribution of procaine following subconjunctival injections of a 1% solution of the hydrochloride salt was studied in albino rabbits. Quantitative chemical analyses of the iris, aqueous, and cornea were made at various time intervals. Higher concentrations of procaine were found in the iris, aqueous, and cornea in freshly killed animals and when epinephrine was added to the anesthetic solution. These data indicate that the conjunctival and episcleral vessels carry the drug solution rapidly from the limbic area and thereby reduce ocular penetration. They also indicate that the anterior ciliary and limbic circulations play a relatively small role in the passage of procaine into the anterior segment from the subconjunctival tissues.

Additional data were obtained to support our contention that evaluation of the ocular penetration of drugs should not be based solely on analyses of the intraocular fluids. Much higher concentrations of procaine were found in the iris and cornea than in the aqueous humor.

In the living animals nearly maximal concentrations of procaine often were not obtained in the iris, aqueous, and cornea until about 10 minutes after subconjunctival injection of the drug solution. These levels could be increased significantly by the addition of epinephrine, but not of hyaluronidase. Even then, the highest concentrations obtained in the iris were below, or barely in the range of, presently known minimal effective concentrations for anesthesia of small sensory nerves. This may explain the differences in opinion regarding the adequacy of iris anesthesia induced by this method in the human eye. It further emphasizes the clinical importance of adding vasoconstrictor drugs and allowing adequate time for penetration after injection. Additional studies with higher concentrations of procaine and with more potent anesthetic agents, such as benoxinate, seem essential if methods are to be developed which consistently will induce adequate anesthesia of the iris by subconjunctival injection.

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Registry of Interesting Cases

It is the purpose of this section to record cases on the basis of interest only. No complete review of the literature is attempted and no claim for priority is implied except when specifically stated. Publication of case reports is subject to the concurrence of the Editorial Board on the interesting aspects of the case. It is requested that the reports submitted be as brief as is consistent with inclusion of the pertinent facts, bear a title that is as specific as possible, be prefaced by a paragraph that states why the author feels the case is of interest and be accompanied with photographs whenever possible.

DETACHMENT OF RETINA WITH USE OF DIISOPROPYL FLUOROPHOSPHATE (FLUROPRYL) IN TREATMENT OF GLAUCOMA

RETINAL detachment as a complication of the treatment of glaucoma with diisopropyl fluorophosphate (Fluropryl; DFP) has been noted in a few cases in the ophthalmologic literature. Because of the rarity of this complication of the use of diisopropyl fluorophosphate, it was thought that the report of such a case would be of interest.

In February, 1951, E. M., a white single 70-year-old woman was seen for a routine eye examination because she had broken her glasses. She reported no previous difficulty with her eyes except that she had worn glasses for several years. She had obtained her present glasses about one year previously.

On ocular examination vision of 20/40—2 in the right eye and 3/200 in the left eye was noted. This was corrected to 20/25 in the right eye and 20/30 in the left eye on refraction with 1.25 sph ⊃ 0.50 cyl, ax 20 (right eye) and —4.50 sph ⊃ 0.75 cyl, ax 10 (left eye). External, extraocular muscle, and fundus examinations were not remarkable. There were a few tiny posterior subcapsular opacities in both lenses. Tension was found to be 34 mm. (Schiøtz) in the right eye and 40 mm. (Schiøtz) in the left eye. Examination of the anterior chamber showed it to be of about average depth. Visual field studies showed a marked loss of upper nasal field and a Bjerrum scotoma in the left eye. The right visual field was normal. A diagnosis of wide-angle or simple chronic type glaucoma was made. The patient was initially treated with 2% pilocarpine four times daily and was continued on this treatment for a period of six months. On this therapy the tension was well controlled in both eyes except on one occasion, when the patient neglected to use the drops for one week. Visual fields in the left eye showed some progression during this period.

The patient moved to another locality and, while away, suffered a cerebral vascular accident. Upon her return, after 15 months, marked visual field changes in the left eye were noted, and it was found that pilocarpine would no longer control the tension. Carbachol U. S. P. was given in addition to the pilocarpine, without benefit. Glaucoma surgery was considered for the left eye but was thought to be contraindicated because of the proximity of the Bjerrum scotoma to the fixation point. The patient was referred to a consultant, who agreed that surgery was not indicated and recommended the use of diisopropyl fluorophosphate in the left eye. The tension was well controlled with this drug, but after three months sensitivity reaction of the lids developed and the medication was discontinued. The patient was once more placed on pilocarpine, 4%, and carbachol, 2%, four times a day. On this treatment the tension remained controlled for a few weeks but again rose to 30 mm. in the right eye and 40 mm. in the left eye. For two months the patient was placed on pilocarpine, 2%, and physostigmine, which controlled the tension but also produced a sensitivity reaction. Once more she was placed on pilocarpine and carbachol. This kept the tension at a borderline level for three months, but she began to show field loss in the right eye.

In October, 1953, diisopropyl fluorophosphate in sesame oil became available for investigative work, and treatment was started with this. Again, the tension was well controlled in both eyes. A mild sensitivity reaction developed, but this cleared with the use of cortisone ointment. On Dec. 12, 1953, the patient reported marked blurring of vision and showed marked loss of the nasal half of her right visual field. A large bullous detachment of the temporal one-half of the right retina was noted. A large tear in the retina was found in the upper temporal quadrant. The patient was hospitalized, and on Dec. 18, 1953, a diathermy reattachment of the retina was done. The postoperative course was uneventful. The retina became reattached. Three months postoperatively the retina was still firmly attached. Vision in the right eye with the proper correcting lens was 20/70 and in the left eye 20/100. The tension in the right eye has remained low, varying between 4 and 20 mm. (Schiøtz).

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Annual Reviews

NEURO-OPHTHALMOLOGY

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VISUAL PATHWAYS

Anatomy.—It is generally stated that the optic tract, in its posterior part, is divided by a groove into a lateral and a medial root, and that this medial root is the commissure of Gudden, joining the two medial geniculate bodies, and is not visual in function but is an auditory commissure. Wolff [1] disagrees with these statements and asserts that (*a*) the groove is shallow, so that there is no sharp division between the medial and the lateral part of the tract, (*b*) both the medial

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and the lateral part of the tract end in the lateral geniculate body, (*c*) there is no evidence that the commissure of Gudden occurs in man, and (*d*) the medial root of the human optic tract is not Gudden's commissure. Since the lateral part of the optic tract is visual in function, the medial part must also be a visual commissure.

Electric Responses.—Burian [2] discusses some of the electric responses of the human visual system. At present the only ones which can be recorded are the responses of the retina to light by electroretinography, and such responses of the visual cortex as may be recorded through electroencephalography. The most interesting observations in the electroencephalogram are the disappearance of the alpha rhythm and the phenomenon of photic driving. The alpha rhythm is a spontaneous rhythmic activity with a frequency of 8 to 13 cps and an average amplitude of about 30 mv.; it is the outstanding component in the electroencephalogram. Attenuation or disappearance of the alpha rhythm occurs when a subject opens his eyes, even in total darkness, or when the eyes are stimulated by light. Photic driving consists of rhythmic potentials evoked in the occipital cortex by repetitive stimulation of the eyes with light, but is not observable in all subjects. Since alpha blocking and photic driving depend upon stimulation of the eyes, the condition of the eyes and of the visual pathways must materially influence both these entities. The combination of electroretinography and electroencephalography offers a promising and fascinating approach to an understanding of the physiology of the visual act. Many of the academic facts known today will be turned into practical clinical use in the future.

Monnier and von Berger [3] determined the conduction time of the visual pathway in man with simultaneous recordings of the electroretinogram and the electrocorticogram of the area striata under the influence of physiological light stimuli acting upon one or both eyes. These authors believe the determination of the retinocortical interval may be of value in the practical localization of cerebral lesions.

Kluyskens and Titeca [4] utilize the principle of alpha blocking in an electroencephalographic method of determining the limits of the visual field and the borders of scotomas. Their results agree satisfactorily with those obtained by ordinary subjective methods of perimetry in normal subjects and in patients with organic lesions involving the visual pathways. Gross discrepancies in the fields plotted by the two methods were found in malingerers and in patients with functional diseases.

Ametropia.—Daenen [5] presents data and visual fields which demonstrate the importance of having the patient wear lenses, correcting the vision for 33 cm., to obtain accurate measurements of the higher isopters on the Goldmann perimeter. Lenses are especially important in cases of aphakia and high myopia.

Color Fields.—Arakawa [6] describes the isopters for red, yellow, green, and blue spectral lights as determined quantitatively by the method of Motokawa. The paper is physiological and technical; no clinical applications are described.

Controversy continues regarding the value of colored test objects in the detection of early visual field defects. Enoksson [7] relates his findings in 10 cases of pituitary tumor verified at operation. He employed a large Bjerrum screen at 1 or 2 meters distance, white test objects of 1, 2, 3, and 5 mm. diameter, and red, green, and blue test objects of 10, 20, 30, and 40 mm. diameter. White objects were charted where they first became visible; each colored test object was charted at the point where the patient recognized its correct color. For comparison, the author selected

white and colored isopters which extended to the same limit in a given meridian in the least affected, or most normal, portion of the field. Twelve visual field charts led him to conclude that there is no significant difference between the fields obtained with white and those obtained with colored test objects. I do not regard this as a justified evaluation of colored test objects. If the extent of the isopter of a colored stimulus is the same as that of a smaller white stimulus in the normal portion of the field, one would also expect the extent of the isopters to be equal in the impaired areas. This means simply that stimuli of equal strength are being used, and the isopters should be identical in both normal and impaired areas of the field. In my experience a red test object has been of superior diagnostic value; patients usually find it easier to judge the absence or presence of a 3 or 5 mm. red object than that of a 1 mm. white object. Despite the theoretical value of the 1:1000 and 1:2000 white stimulus, stressed by numerous authorities, the test is truly a difficult one for the patient, as one can confirm by trying the test on himself.

Optic Neuritis.—It is generally taught that optic neuritis usually impairs visual acuity and produces a central scotoma, and only rarely spares the fixation area. To determine the incidence of fixation sparing, Chamlin [8] selected 100 cases of optic neuritis, in most of which the etiological factor was not established, and found that at least 21%, and possibly as many as 37%, of the cases had normal, or nearly normal, visual acuity. He concludes that the preservation of central acuity alone must not be used as a major criterion in the differential diagnosis of optic neuritis. One should note that the author does not state the level of visual acuity in these 37 cases, and also that the statistical analysis employed the earliest visual defect observed. It would be informative to know whether the visual acuity decreased during the later course of these cases.

Gartner [9] reports the histological findings in 14 eyes obtained from 10 cases in which the diagnosis of multiple sclerosis was confirmed at autopsy. The optic nerves showed irregular atrophy, involving predominantly the papillomacular bundle and the temporal side of the nerve, but affecting peripheral fibers also. There was an increase in cells, especially the glial cells, in the nerve. The disc surface and adjacent area showed extensive gliosis, corresponding to the clinical appearance of secondary optic atrophy. The blood vessels on and near the disc were thickened and sclerosed. The retina revealed atrophy of the nerve fibers and ganglion cells, observed most readily at the macula. It appears that the optic nerves are involved in a high percentage of cases of multiple sclerosis, and that almost all the patients will develop ocular involvement if they live long enough. Some damage probably remains after any recovery from an acute attack of optic neuropathy but may be undetected unless careful functional testing is employed. It is frequently stated that one attack of optic neuritis is the rule and that recurrences are uncommon. From the evidence of extensive atrophy of the nerve seen pathologically, Gartner suggests that there have been repeated attacks, unobserved by the patient, in many cases. Although the optic nerves were involved in all 10 cases, in only 2 was the acute optic neuropathy diagnosed during life. This may be due to lesions affecting the peripheral fibers, producing defects unnoticed by the patient; or the presence of nystagmus, diplopia, or mental deterioration could easily obscure the presence of an attack of optic neuropathy.

Taub and Rucker [10] report on 87 patients who had had acute retrobulbar neuritis of unknown origin and who were followed for 10 to 15 years. In 32% (28 patients) multiple sclerosis developed. Twenty-six of the patients were between 20 and 44 years of age at the onset of the optic neuritis. The authors conclude that a patient having retrobulbar neuritis between these ages has a 50% chance of developing multiple sclerosis, whereas a person under 20 or over 44 years of age has only a remote chance of developing the disease.

Schlossman and Phillips [11] report that the optic neuritis in 50 of 72 patients (69%) was due to multiple sclerosis. This high incidence is attributed to the fact that the patients were followed in a hospital for chronic diseases and were observed over a long period of time.

Fine and Flocks [12] report the case of a man, age 29, who suffered severe bilateral neuroretinitis; the acuity was reduced to 20/400 in the right eye and to perception of hand movements in the left eye. Biopsy of an axillary lymph node revealed sarcoidosis. Treatment consisted of oral cortisone and intravenous corticotropin for one month. The acuity improved to 20/20 in each eye after five months.

McReynolds, Havener, and Petrohelos [13] report the case of a girl, age 7 years, who developed bilateral papillitis two weeks after a booster dose of diphtheria-tetanus toxoid and a smallpox vaccination. The acuity was reduced to 6/100 in the right eye and to absence of light perception in the left eye. There were no neurological signs. She was treated with corticotropin. Two months later the acuity had improved to 20/20 in each eye and the optic discs appeared normal.

Tanner [14] reviews the literature on the ocular manifestations of infectious mononucleosis and reports a proved case in a 17-year-old girl. He states that the patient had bilateral iridocyclitis and papilledema. The visual acuity, however, was not taken until the 13th day of the illness, when it was found to be 20/30; on the 26th day it was 20/20. Fields were said to be normal, but there is no description of them. The differential diagnosis of papilledema due to increased intracranial pressure and papillitis due to inflammation was not, and can not, be made without determinations of the visual acuity earlier in the disease, accurate tangent screen studies, and measurements of the spinal fluid pressure.

Optic Nerve Tumors.—Marshall [15] reports the case of an 8-year-old girl who had systemic von Recklinghausen's disease and a glioma of the right optic nerve. The association of these two conditions has been known for many years, but the paper serves to remind us of this relationship and summarizes the clinical manifestations of the two diseases.

Manschot [16] reports two siblings who had glioma of the optic nerve and chiasm and signs of systemic von Recklinghausen's disease. He states that the relation between optic nerve tumors and neurofibromatosis has not yet become generally known.

It is well to remember, as Christensen and Andersen [17] warn, that an orbital tumor in a patient with neurofibromatosis is not necessarily an optic nerve glioma. It may be a neurinoma or fibroma of perineural origin.

Trueman and Rubin [18] report a case of tumor of the right optic disc in a patient with neurofibromatosis. They do not state, but imply, that it was a neurofibroma. This is the third such case reported in the literature.

Miller and Van Herick [19] report bilateral primary optic atrophy in a man, age 42, with neurofibromatosis, but they do not state the cause of the atrophy.

Sphenoid Ridge Meningioma.—Kearns and Wagener [20] analyzed the symptomatology of 106 cases of surgically or pathologically proved meningiomas of the sphenoid ridge. A hypothetical case composed of the commonest signs would be that of a 40- to 50-year-old woman with unilateral progressive loss of central vision, a prechiasmal type of field defect, homolateral exophthalmos, and optic disc pallor. Less frequent are papilledema, pupillary dilatation, ocular muscle palsies, and pain. X-rays often, but not always, reveal hyperostosis of the sphenoid ridge. The ophthalmologist should be alert to suspect this lesion in a case of unexplained impairment of central vision or progressive exophthalmos in one eye, because neurosurgical cure depends upon early diagnosis.

Schaerer and Whitney [21] report the case of a man, age 71, who developed loss of vision, papilledema, and exophthalmos in the right eye in four months. The skull appeared thickened, deep to the right temporal muscle. X-rays revealed hyperostosis of the bones of the right orbit and the entire right sphenoid wing. The clinical diagnosis of meningioma en plaque of the sphenoid wing arising from the pterion appeared justified. Craniotomy was performed to decompress the right optic nerve. Biopsy specimens, surprisingly, revealed metastatic carcinoma. Metastases found in the vertebrae and pelvis were characteristic of carcinoma of the prostate, and the diagnosis was confirmed by rectal examination. The features superficially resembled a meningioma en plaque, but the authors believe the diagnostic error would have been prevented if proper evaluation had been given to the rapidity of the visual loss, the patient's age and sex, and the x-ray evidence of hyperostosis involving also the zygomaticotemporal process.

Optic Chiasm.—In the early stages of evolution of a pituitary tumor the superior bitemporal hemianopia is due to direct pressure of the tumor on the optic chiasm or to interruption of its blood supply. In the later stages the defects in the inferior temporal and inferior nasal quadrants may be caused by the tumor pressing the optic nerves upward against the margins of the bony optic canals, or by pressing the optic nerves and chiasm upward against the overlying anterior portion of the arterial circle of Willis. Rucker and Kernohan [22] describe five cases, with accompanying photographs of necropsy specimens which clearly depict the deep notching extending transversely across the optic chiasm and optic nerves due to pressure of the overlying anterior cerebral and anterior communicating arteries.

Homonymous Hemianopia.—It is generally recognized that homonymous hemianopia is an extreme rarity in multiple sclerosis. This seems strange, considering the frequency with which the optic nerves and chiasm are affected. Chamlin and Davidoff [23] report four cases of homonymous hemianopia in which the features supported a clinical diagnosis of multiple sclerosis; this diagnosis was not confirmed by necropsy. Three of the patients showed dense paracentral components in the hemianopic fields, and on this basis the authors suggest that when multiple sclerosis does involve the retrochiasmal pathways, the site of involvement is near the occipital visual cortex.

Anoxia and Cortical Blindness.—Foley and Paterson [24] report the case of a 25-year-old woman who had apnea lasting four minutes during a severe asthmatic

attack. Extensive cerebral damage resulting from the anoxia affected the motor areas, basal ganglia, cerebellum, and parieto-occipital areas. Cortical blindness was permanent.

Givner [25] warns that visual loss following cardiac arrest and reactivation of the heart will be encountered with increasing frequency, owing to the increasing number of recoveries resulting from heart massage. He reports the case of a boy, age 8 months, in whom the visual loss seemed attributable to edema of the visual cortex, rather than to local retinal pathology.

Time Factor in Visual Field Defects.—The visual act is traditionally regarded as consisting of two processes. The first process, subserved anatomically by the visual pathways extending from the retina to the striate area in the occipital cortex, is physiological, and transforms peripheral light stimuli into elementary sensations. The second process, relegated to the higher visual areas in the occipital and parietal lobes, is psychological, and integrates the elementary sensations into final visual perceptions. Impairment of the first process results in visual field defects; impairment of the second process produces visual agnosia. A more accurate analysis of the nature of visual field defects and a revolutionary concept of the nature of visual agnosia are presented in a complex paper by Bay.[26] His refreshing and challenging ideas command serious consideration but will be appreciated most by physicians who do their own field studies on neurological patients.

Ordinary field studies are quantitative; that is, an isopter for a given stimulus delimits the area in which the stimulus is seen from the area in which it is not seen. The answers are either "yes" or "no." Bay signals our attention to the importance, in both normal and pathological perceptions, of the time factor; this is disregarded in conventional campimetry. The most practical test is based upon the phenomenon of local adaptation. If a stationary test object is maintained constantly in the peripheral field, the perception of this stimulus slowly fades and eventually ceases. The length of time from exposure of the stimulus to its disappearance is termed the "fading time." The fading time is short in the periphery and increases toward the center of the field; in the fixation area large objects do not disappear at all. The test of local adaptometry is performed by exposing simultaneously two equal stimuli on symmetrical points of the tangent screen. The time of disappearance of each stimulus is measured with a stop watch. In pathological cases the fading time is decreased. Curves for the normal and the abnormal fading times for a given meridian are plotted on a graph; from these a "damage curve" is drawn, which indicates the amount of functional impairment in any given area.

From studies of patients both by ordinary campimetry and by local adaptometry, Bay concludes that local adaptometry is the superior method; he considers that it provides a more accurate and more complete evaluation of visual impairment, a more reliable localization of the lesion, and a finer understanding of the nature of visual dysfunction in the macular area. These points are defended in several illustrative cases.

Case A.—A shell fragment injured the left optic tract. A complete right homonymous hemianopia with splitting of the macula, and completely intact left homonymous fields were found both by ordinary campimetry and by local adaptometry. This is as expected in a tract lesion.

Case B.—A missile injured the anterior portion of the left optic radiation. The left homonymous fields were found intact by both methods. Ordinary campimetry showed a right

homonymous hemianopia with macular sparing. Local adaptometry, however, demonstrated considerable decrease in fading time in the area of macular sparing. The damage curve indicates, therefore, that the entire right half-fields were impaired and, furthermore, that the functional loss was greatest in the macular area.

CASE C.—In a case of injury to the right occipital region, ordinary campimetry showed a left homonymous hemianopia with macular splitting and intact right half-fields. This is the same type of field defect as that found in Case A. Local adaptometry revealed a difference between the two cases; in Case B it showed severe damage in the apparently intact right homonymous fields, with maximal loss in the macular area. This case illustrates that the macula is not always spared in occipital lesions and that local adaptometry revealed more extensive impairment than did ordinary campimetry; this, in turn, indicated impairment of both occipital lobes, thus differentiating the lesion from one of the optic tract.

CASE D.—In a case of injury in the region of the inion, ordinary campimetry showed a right homonymous paracentral scotoma. Local adaptometry revealed serious functional damage in the entire macular area, but greater in the right half than in the left. Thus, despite normal visual acuity, the patient was severely handicapped.

CASE E.—In a case of a depressed fracture of the inion, ordinary campimetry showed a right homonymous hemianopia with macular splitting and normal acuity, but local adaptometry revealed severe impairment of the entire macular area.

These cases demonstrate that the macular area is always more severely impaired than is indicated by ordinary campimetry. In parietal and occipital lesions the damage curve discloses that the maximal functional loss is in the macular area—an illustration of Hughlings Jackson's law that disintegration of cerebral functions begins, and is severest, on the highest functional level. The functional level of the fovea is so high above that of the retinal periphery that the residual function of the macular area, despite its greater damage, is still superior to the peripheral parts and consequently appears to be better preserved in ordinary campimetry. This seeming contradiction that the apparently best-preserved area is actually the most severely damaged is explained by the high functional superiority of the fovea over the periphery.

Thus, "macular sparing" originates from the high functional level of the central parts, and not from a bilateral anatomical connection of the macular fibers. The function in the area of macular sparing is always impaired, and is never normal.

The steady course of the damage curve, shown by the smooth transition from point to point, cannot be explained by corresponding steady pathological changes in the underlying lesion. This discrepancy is incompatible with the generally accepted theory of a rigid and distinct point-to-point projection of retinal elements in the striate area. Bay agrees with von Monakow in the concept that the fovea is represented in the whole striate area; its representation is not uniform, but shows preference for the area near the occipital pole, where it is isolated from the peripheral field. The anterior parts of the striate area contain a weaker representation of the fovea, together with representation of the periphery. This would explain anatomically the fact that central vision is always impaired, but never completely abolished, before the peripheral vision. Never has Bay found a complete loss of central vision if any peripheral vision remains.

HIGHER VISUAL DISORDERS

Visual Agnosia.—The textbooks classically differentiate between the physiological and the psychological processes in perception and define visual agnosia as a disturbance in the psychological process whereby a patient is unable to recognize

objects, although the visual acuity, visual fields (elementary sensations), and mentality are normal. Bay [26] cannot agree with this traditional concept and states that there does not exist in the literature a single case of agnosia without disorders in the elementary sensations (visual pathways) and without mental impairment. He cites the case of a 60-year-old man who developed visual agnosia, although the acuity and fields in his left, and only, eye appeared normal by ordinary campimetry. This would appear to be a case of pure visual agnosia. Local adaptometry, however, disclosed a nasal hemianopia. Tachistoscopic determinations of the sensation time (the minimal time required for the appearance of a sensation) demonstrated severe impairment in the perception of subtle patterns and fine shades of texture and tint which are essential for the identification of most objects. Thus, the patient "could see everything" but could not recognize objects because he could not perceive details. During recovery from the illness there was strict correlation between the so-called higher gnosic functions and the physiological functions as determined by tachistoscopy and local adaptometry.

Bay is convinced that there is no such entity as visual agnosia, that the classic concept of agnosia is not based upon exact and reliable information, that there is neither a specific gnosic function nor a specific disorder of this function, and that so-called visual agnosia is due to an impaired primary visual system combined in most cases with a greater or less degree of general mental deterioration. Objects are seen imperfectly and assessed inadequately.

Visual agnosia has frequently been subdivided into many individual types, such as alexia (inability to recognize letters), simultanagnosia (recognition of single objects with inability to conceive the meaning of their combination), prosopagnosia (inability to recognize a person's face), Gestalt dissolution (an object is at first seen whole and soon appears scattered into its single components), and the various types of visual spatial agnosias. Bay does not believe that such specific types occur in pure form; a particular type cannot occur in isolation.

Parietal Lobes.—Critchley [27] has written a superb monograph, destined to become a classic, on the parietal lobes. Current neurology is giving considerable attention to the rich variety of clinical phenomena resulting from disease of the parietal and occipital lobes. The visual disorders are especially interesting. An understanding of the nature of the visual agnosias is particularly promising in explaining the problems of cortical localization. Patients are characteristically unaware of, or actually deny, the diverse and incapacitating symptoms. Most parietal signs are not revealed by routine examination but are elicited by numerous special qualitative tests. In fascinating style, the author discusses cortical blindness, denial of blindness, nonawareness of hemianopia, color agnosia, visual object agnosias, prosopagnosia, numerous varieties of metamorphopsia of central origin, visual perseveration, dyslexia, visual disorientation, defective revisualization, visual inattention, altered adaptation time, optokinetic nystagmus, altered rate of flicker fusion, tachistoscopy, acalculia, and dysgraphia. Critchley remarks that no artificial distinction between lower and higher visual functions is deemed advisable, or even possible, and believes that the traditional concept of agnosia is being drastically modified and is in the process of being rejected altogether.

Paralexia.—Lyle [28] reports five cases and discusses the symptom of difficulty in reading, or paralexia, in which there is a failure to see the right- or left-hand

letters or syllables of a word. A right or left homonymous hemianopia would appear to be the logical explanation of the reading impairment. Analysis of the cases reveals, surprisingly, that a homonymous field loss is not necessarily present; furthermore, the patient may have a homonymous hemianopia with normal acuity and have no difficulty in reading. The constant finding is the absence of optokinetic nystagmus on rotating the drum toward the side of the lesion. A patient with normal optokinetic nystagmus does not experience this reading difficulty, whether or not he has hemianopia. Lyle believes the responsible lesion involves the occipitomesencephalic tract. This tract arises in Areas 19, 18, and possibly 17 and passes anteriorly in the internal sagittal stratum, adjacent to the fibers of the optic radiation, courses into the brachium of the superior colliculus, and terminates in the tectum of the midbrain; here, crossed and uncrossed fibers connect the tract with the nuclei of the oculomotor nerves. The chief action of this tract has to do with fixation and following movements and probably aids in continuous and smooth reading.

Heidenhain's Syndrome.—Meyer, Leigh, and Bagg [29] report the case of a man, age 38, who developed forgetfulness, difficulty in concentrating, irritability, headaches, and failing vision. He was confused and disoriented and suffered memory impairment. The neurological examination, including the cranial nerves, and laboratory studies were otherwise negative. Dementia and blindness developed rapidly, and the patient died six months after the onset of symptoms. Necropsy revealed diffuse degeneration of the cortex in all regions, but the severest changes were in the occipital lobes, where the convolutions were markedly atrophic. Since this case resembles two cases published by Heidenhain in 1929, the authors suggest that this combination of a rapidly fatal illness characterized by progressive presenile dementia and cortical blindness be called Heidenhain's syndrome. The features of the presenile dementias and the differentiation from Alzheimer's disease, Pick's disease, and the Creutzfeld-Jakob syndrome are discussed.

Hallucinations in Braille.—Visual hallucinations are uncommon in the blind, and there is no known reference to hallucinations in symbols. For these reasons, the report of Freeman and Williams [30] is unusually interesting. A woman, age 30, blind since 13 years of age, had a schizophrenic reaction with hallucinations of hearing and seeing. The visual hallucinations were predominantly in Braille code. After unilateral amygdaloidectomy the hallucinations disappeared.

PAPILLEDEMA

Diagnosis.—The difficulties of diagnosing true papilledema are briefly discussed by Lyle [31] in a refreshing paper. Errors are due usually to failure to examine the fundi through dilated pupils, lack of experience and familiarity with normal variations and anomalies of the optic disc, failure to determine the visual acuity and visual fields, and failure to consider the patient as a whole, with regard for all other ocular, neurological, and medical findings. Lyle prefers the term "optic-disc-edema" to refer to edema of the disc, irrespective of its cause. Personal experience is in agreement with his statements that it is extremely difficult in some cases to give a confident opinion as to the absence or presence of early disc edema, and that it is undesirable to make an emphatic statement as to the absence or presence of edema unless the examiner is reasonably certain of his conviction.

Glomus Jugulare Tumors.—Tumors of the glomus jugulare (nonchromaffin paraganglioma of the middle ear) usually cause aural symptoms and have been reported frequently by otologists. Biopsy of the mass presenting in the external auditory meatus confirms the diagnosis. In recent years a few cases showing neurological manifestations have been reported. Clinically, after an initial period of otological symptoms, there develop a succession of paralyses of the lower cranial nerves (VI to XII) and homolateral cerebellar signs as the tumor invades the middle and posterior cranial fossae. Symptoms of increased intracranial pressure are rare.

Since authors have remarked on the absence of papilledema in all cases of this tumor, it is interesting to read the report of Hierons and Meadows.[32] They relate the case of a woman, age 38, whose presenting symptoms were transient episodes of blurred vision and frontal headaches. There was no deafness. There were bilateral papilledema and palsy of the lower cranial nerves on the left side. Biopsy of a dark-blue vascular mass in the left auditory meatus revealed a tumor of the glomus jugulare. Ventriculography disclosed a large tumor in the left cerebellopontine angle. Meadows has since seen two other cases of this tumor with papilledema.

In an excellent discussion of the pathology and classification of glomus jugulare tumors, Zak [33] reports two surgically verified tumors in the posterior and middle fossae, respectively. Early papilledema was present in the latter case.

Hypoparathyroidism.—Grant [34] reviews the literature and reports three cases of papilledema occurring in chronic parathyroid tetany. This syndrome of papilledema in hypoparathyroidism, in most cases resulting from thyroidectomy, is rare. The clinical importance is stressed because the combination of epileptiform seizures in a patient with papilledema and increased intracranial pressure immediately suggests a brain tumor. Generalized cerebral edema, of unknown cause, is present. Treatment with calciferol or dihydrotachysterol is satisfactory.

In a valuable review of ocular manifestations due to abnormal calcium metabolism, Walsh and Murray [35] also advise that unexplained papilledema, with or without convulsions, may be due to hypoparathyroidism. The presence of a low blood serum calcium will clarify the diagnosis and eliminate the indication for air studies, arteriography, and craniotomy.

Guillain-Barré Syndrome.—Krohn [36] reports the case of a man, age 21, who developed bilateral papilledema during the course of polyradiculoneuritis involving the lower extremities (Guillain-Barré syndrome). Papilledema is very rare in this condition and may be related to the unusually high spinal fluid protein, found to be 248 and 624 mg. per 100 cc. on two occasions.

Poliomyelitis.—Murray and Walsh [37] state that it is not well known that papilledema may develop in poliomyelitis, since fundus examinations are usually made only during the early stages of the disease, whereas papilledema characteristically appears later, during the recovery phase. The cause is unknown but may be related to the high spinal fluid protein. The papilledema persists for weeks or months and subsides without visual impairment. Experimental, clinical, and necropsy data disprove the occurrence of papillitis; reported cases of papillitis are actually cases of papilledema. The authors found ocular complications, such as muscle palsies and pupillary abnormalities, in only 17 of 516 cases of poliomyelitis. It is disappointing to find that they do not state whether or not they personally observed papilledema in any of these cases. Their conclusions appear speculative and are based upon a review of the literature.

Increased Spinal Fluid Protein.—Gardner, Spitler, and Whitten [38] relate the case of a woman, age 52, whose presenting complaint of failing vision was due to an ependymoma of the cauda equina! The spinal fluid pressure was 325 mm. of water, and its protein content was 425 mg. per 100 cc. Bilateral papilledema with secondary optic atrophy impaired the vision in both eyes. A second woman, age 44, complained of fainting spells and headaches. Nystagmus on right gaze was the only neurological sign. Spinal fluid pressure fluctuated from 180 to 400 mm. of water, and the protein level was 400 mg. per 100 cc. Pneumoencephalography revealed a communicating hydrocephalus. Suboccipital craniotomy disclosed a 2 cm. acoustic neurilemmoma. A third woman, age 26, with the Guillain-Barré syndrome, developed paralysis of the lower extremities, facial paralysis, and bilateral papilledema. The spinal fluid pressure was 600 mm. of water, and the total protein was 470 mg. per 100 cc. On the basis of these cases, and similar ones in the literature, the authors believe that increased intracranial pressure can result from any chronic process that significantly raises the protein content of the cerebrospinal fluid. Serum protein transudes through the imperfect walls of a tumor, though small, located anywhere along the cerebrospinal axis. The numerous large protein molecules in the spinal fluid mechanically clog the pores of the semipermeable membrane that constitutes the brain-blood barrier; absorption of spinal fluid is delayed, with resulting increase in intracranial pressure, communicating hydrocephalus, and papilledema. A similar process may operate in the Guillain-Barré syndrome and in poliomyelitis.

Pseudotumor Cerebri.—Wagener [39] reviews the literature on pseudotumor cerebri, referred to variously as otitic hydrocephalus, meningeal hydrops, and cerebral edema. He recommends the term "intracranial hypertension of unknown cause" until the etiologic factors can be proved. Although thrombosis of the dural sinuses, especially of the superior longitudinal sinus, can produce cerebral edema, other causes should be considered in the differential diagnosis.

Posner [40] reports the interesting case of a man, age 34, who developed acute glaucoma in both eyes during the acute phase of meningeal hydrops. The optic disc were essentially normal. The intraocular pressure was normalized in 24 hours with pilocarpine drops; these were discontinued after 4 days. The pupils were dilated for fundus study, which revealed bilateral papilledema. The pressure remained normal without miotics, and the papilledema had nearly subsided after two months. The author speculates whether or not the increased ocular tension suppressed the development of papilledema, which appeared shortly after the tension was normalized.

PUPILS

Horner's Syndrome.—It has long been recognized that the clinical manifestations of Horner's syndrome are variable, not only in different patients but at times in the same patient. Ehlers [41] describes these variations, reviews the anatomy of the sympathetic nerve pathways, and discusses the theories advanced over the years to explain the clinical variations. The theories are based upon the developmental stages of the syndrome, the localizations of the lesion within the pathway, and the individual variations of the sympathetic pathways (sympathicoschisis). The author's theory is that of retardation of the sympathetic response, in which the time factor is an important element.

Anisocoria in Migraine.—Jacobsen [42] studied the pupillary manifestations in 28 patients, including himself, with paroxysmal unilateral migrainous headaches of the vasodilatory type. During the attacks the homolateral pupil became smaller than the pupil on the unaffected side. He interpreted this as indicating homolateral hypofunction of the sympathetic nerves. In some patients, between the attacks the homolateral pupil was larger than the other pupil; this phenomenon is known as alternating anisocoria.

The naso-ocular reflex in normal persons consists of bilateral lacrimation and conjunctival hyperemia following unilateral irritation of the nasal mucosa and is said to be due to sympathetic inhibition. The unilateral occurrence of the ocular manifestations is interpreted as a decreased function of the homolateral cervical sympathetic nerves and is known as sympathicoschisis. Jacobsen [43] found that the majority of patients (31 of 35) suffering from unilateral migrainous headache of the vasodilatory type show a homolateral naso-ocular reflex.

Thus, patients suffering with vasodilatory migraine may exhibit homolateral miosis and a homolateral naso-ocular reflex, due to sympathetic paresis. Clinically, the combination of homolateral head pain and miosis immediately suggests the possibility of Raeder's paratrigeminal syndrome.

Adie's Syndrome.—Sprofkin [44] calls attention to the value of the methacholine (Mecholyl) test of Scheie in the recognition of Adie's tonic pupillary syndrome. In one case Adie's syndrome was found in a psychoneurotic woman. In a second case the presence of progressive left-sided weakness and a dilated left pupil raised suspicion of an intracranial tumor; the positive methacholine test and other neurological signs justified the diagnosis of Adie's pupil in a patient with amyotrophic lateral sclerosis. In the third case the history of alcoholism, cranial trauma, and headache, and the presence of a semidilated left pupil, suggested a subdural hematoma; the positive blood serology and the history of antisyphilitic therapy suggested an Argyll Robertson pupil; the final diagnosis was late latent syphilis and Adie's syndrome.

Brunnschweiler [45] studied the methacholine test in 100 eyes that definitely did not show a pupillotonic reaction and found that some normal pupils react to methacholine, and that some of the normal pupils were dilated instead of constricted. A miotic reaction to 2.5% methacholine chloride cannot be considered as a definite sign of pupillotonia; however, a strong miotic reaction, with a thorough clinical examination, is of great value in differential diagnosis.

MUSCLES

Progressive External Ophthalmoplegia.—Increasing interest in the problem of the etiology of chronic progressive external ophthalmoplegia is evidenced by the detailed neuropathologic study of a case by Schwarz and Liu.[46] In their patient, who died at age 63, ocular symptoms had begun at age 28 and progressed to bilateral ptosis and nearly complete paralysis of all the extraocular muscles. There were no significant pathological changes in the oculomotor, trochlear, or abducens nuclei or nerves. The extraocular muscles showed changes compatible with those found in muscular dystrophy. A significant contribution is their observation that the intramuscular nerve fibers were abundant and that motor end-plates were identified in the degenerated muscles. The authors conclude that their studies support the opinion that this condition is a form of muscular dystrophy and is not a neuronal disease.

Wernicke's Disease.—In 1881 Wernicke described a fatal illness characterized by a triad of signs including mental disturbances, ataxia of gait, and ophthalmoplegia. He considered it to be inflammatory in nature and named it "acute superior hemorrhagic encephalitis." It is now accepted that the disease is due to a specific lack of thiamine and that the pathological lesions, not necessarily hemorrhagic, are widely disseminated throughout the brain stem. The nutritional deficiency develops most commonly in a chronic alcoholic but can occur in malnutritional conditions, such as gastrointestinal cancer. Cogan and Victor [47] describe the ocular signs observed in five cases. The ocular signs are the most constant finding and must be present to make the diagnosis clinically.

The mental disturbances take the form of a quiet confusional state, which usually resolves itself into a Korsakoff psychosis. The ataxia is one of stance and gait, although individual movements of the limbs are unaffected; peripheral neuropathy may mask the ataxia.

The ocular signs consist of nystagmus, lateral rectus muscle palsy, and palsy of conjugate gaze. The nystagmus may be the earliest and only ocular sign, and may be horizontal or vertical or both. The lateral rectus muscles may exhibit mild paresis or complete paralysis. Conjugate gaze palsy may also vary in severity from nystagmus on extreme gaze to complete loss of movement. Gaze palsy may be of the horizontal, vertical, or combined type. One should appreciate that the nystagmus in both eyes becomes less noticeable as the conjugate gaze paralysis becomes more profound; similarly, paralysis of a lateral rectus muscle will obscure the nystagmus of the involved abducting eye in lateral gaze. The ocular motor signs were bilateral but not always symmetrical.

Although the ocular signs described can occur in numerous other diseases of the brain stem and cerebellum, the characteristic of Wernicke's encephalopathy is the association of the ocular motor signs, with ataxia, and with the mental disturbances, evolving rapidly upon a background of malnutrition, usually in an alcoholic. The recognition of the disease is of practical importance because administration of thiamine saves the patient's life. Improvement of the ocular signs is evident within a few hours. Less pronounced improvement occurs in the ataxia and nystagmus, and least improvement in the mental state. It is interesting that ptosis, pupillary disturbances, and ophthalmoscopic abnormalities are rare.

Ocular Motor Apraxia.—Ocular motor apraxia is a distinct entity, characterized by loss of volitional control of conjugate gaze but with preservation of full random movements. Only a few cases have been reported. The paper by Cogan and Adams [48] describes two cases in detail and is a valuable contribution because one of their cases is the first of its kind reported with necropsy. In Case 1, a Negro woman, age 27, on the fifth postpartum day developed cerebral paraplegia with left brachial monoplegia, without sensory loss, aphasia, or visual field defect. There was apraxia of her limbs, trunk, head, face, and eyes; the patient knew what she wanted to do but could not do it. Random, and apparently purposeless, movements of the eyes were retained, whereas movements on command were abolished. The clinical diagnosis was thrombosis of the anterior half of the sagittal sinus and cerebral veins, involving the superior and paramesial parts of the frontal lobes. Eye movements were normal by the 24th day. In Case 2, a housewife, age 32, gradually developed left hemiplegia and stupor. During the first week the eyes could be turned to fixate

accurately on an object in the right visual field, either spontaneously or on command; but there was slowness and inaccuracy of response when she was commanded to look to the left, as compared with response on gaze to the right. There were, however, random and purposeless movements of the eyes to the left. This case was one of true and unilateral apraxia of the eyes; no apraxia other than that of the eyes was noted. Ventriculography and craniotomy revealed a large tumor near the midline in the right parietal and posterior frontal regions; necropsy proved this to be a secondary ovarian carcinoma.

In simple paralysis of conjugate gaze there is impairment of both voluntary and random movements of the eyes; the patient's attention and effort tend to overcome the defect. In ocular motor apraxia, however, a full range of random movements is retained, but the eyes cannot be purposefully rotated in the desired direction; the harder the patient tries to turn his eyes in a desired direction, the more he is unable to do so. The apraxia appears to involve a higher order of conjugate control and is more strictly limited to the sphere of volitional control. The authors conclude that the lesion responsible for ocular motor apraxia is apparently located in the premotor area of the frontal lobe.

NYSTAGMUS

Dysmetria; Oscillations; Opsoclonus.—Cogan [49] describes three unusual and rarely described ocular motor phenomena and interprets their clinical and pathological manifestations. They are included at this point to emphasize the importance of differentiating them from the various types of nystagmus.

A. Ocular motor dysmetria is characterized by a consistent overshooting of the eyes on attempted fixation, followed by several oscillations of progressively diminishing amplitude until accurate fixation is attained. It may occur on change of fixation from the primary to an eccentric position, but is usually most striking on refixation from an eccentric position back to the primary position. The overshoot usually disappears in extreme eccentric gaze probably because in lateral gaze the eyes approximate their full power of rotation, so that any tendency to overshoot is masked. In six cases the lesions involved the cerebellum. The overshoot may be lateralized or symmetrical, even with unilateral lesions. Cogan believes the sign has great localizing value, since he has seen it only in lesions involving the cerebellum or cerebellar pathways. It is not present in all cases of cerebellar disease but perhaps is not recognized unless specifically searched for.

B. Flutter-like oscillations are characterized by episodic cycles of pendular movements in the horizontal plane, occurring spontaneously or with changes in fixation, lasting only a few seconds, and recurring several times a minute. They differ from ocular dysmetria in that the cycles are of equal amplitude and may occur spontaneously. All the 11 patients with oscillations had cerebellar disease. Apparently, the cerebellum is normally concerned in the arrest of eye movements in the act of attempted fixation, and in the maintenance of fixation that has been attained.

C. Opsoclonus refers to continual, dancing, totally irregular conjugate movements of the eyes in horizontal, vertical, and rotatory directions ("chaotic agitation"). It is not indicative of cerebellar disease but occurs in certain cases of encephalitis; it should, therefore, be differentiated from ocular dysmetria and flutter-like oscillations.

Retraction Nystagmus.—Lyle and Mayfield [50] report the striking ocular signs in the case of a boy, age 16, admitted in a semistuporous state. There was nystagmus of an irregular type, varying in frequency and amplitude and occurring in paroxysms. With acceleration of the nystagmus, both globes retracted into the orbits, with consequent narrowing of the palpebral apertures. Following movements were normal in all directions of gaze, but there was paralysis of upward gaze for command or request movements; convergence was poor. The retractions of the globes seemed to be instigated by attempted upward gaze or by convergence. The pupils were round and equal in size but reacted poorly to light. Bilateral papilledema was present.

Ventriculography revealed a tumor mass, containing flecks of calcium, in the posterior part of the third ventricle, with dilatation of the anterior part of the third ventricle and of both lateral ventricles. Craniotomy revealed a pinealoma filling the posterior one-third of the third ventricle and extending through the aqueduct of Sylvius into the fourth ventricle. The hypothalamus and midbrain structures were compressed. On the following day necropsy revealed that the neoplasm had also invaded the gray matter and had damaged the oculomotor and trochlear nuclei and the medial longitudinal fasciculus on both sides. The authors give a bibliography of all reported cases, only 20 in the literature, of nystagmus retractorius. One-third were due to brucellosis; one-third were caused by neoplasms in the upper brain stem; the others, by such conditions as Echinococcus cyst, multiple sclerosis, syphilis, and trauma. The constant symptoms of this syndrome, due to lesions involving the aqueduct of Sylvius and the adjacent white and gray matter, are retraction of the eyeballs, paralysis of upward gaze, paralysis of convergence, loss of pupillary light reflex, and incoordination of eye movements with irregular nystagmus.

Streptomycin Toxicity.—Sannella [51] claims priority in his report of an early symptom of streptomycin toxicity, observed in two ophthalmologists, each 31 years old. On moving his head, each patient observed apparent slight motion of objects in a direction opposite the head movement. The symptom appears days to weeks before the signs of gross vestibular damage and may subside if streptomycin therapy is discontinued. The author states that this symptom, if confirmed in more cases, may be a valuable guide to discontinuing therapy before irreversible damage is done to the vestibular apparatus.

TRIGEMINAL NERVE

Corneal Reflex.—It is generally considered that the corneal reflex depends only upon a lower neuron arc through the ophthalmic division of the trigeminal nerve, internuclear neurons, and the facial nerve; and that loss of this reflex indicates interference with this lower pathway. From surgical data and case studies, Oliver [52] concludes that the reflex involves also pathways which pass to the cerebrum. The afferent impulses pass along pain (not touch) fibers in the trigeminal nerve and its descending tract, as shown by the homolateral corneal anesthesia resulting from incision of this tract in the medulla oblongata for trigeminal neuralgia. The reflex path then crosses to the opposite side and ascends in the brain stem, as shown by the contralateral corneal anesthesia following midbrain spinothalamic tractotomy for intractable pain; in this case the corneal sensitivity would be intact if it depended solely upon a lower neuron pathway. The author reports contralateral corneal anesthesia in three cerebral hemisphere lesions (one intracerebral hematoma and two

glioblastoma multiforme tumors) and concludes that the corneal reflex is not simply a lower neuron reflex but depends also upon pathways passing to the cerebrum. This phenomenon of contralateral corneal hypalgesia or analgesia of central origin may prove to be of practical value, for Oliver states he has never observed it in a surface lesion, such as a meningioma or subdural hematoma.

VASCULAR MANIFESTATIONS

Retinal Periphlebitis in Multiple Sclerosis.—Retinal periphlebitis was usually attributed to tuberculosis, sarcoidosis, or sepsis until 1944, when Rucker [53] first showed that sheathing of the retinal veins constitutes a real sign of multiple sclerosis. He found sheathing in 10% of multiple sclerosis patients. Haarr [54] observed periphlebitis in 22.8% of patients with multiple sclerosis and recognized two types. Active periphlebitis may appear during the active phase of multiple sclerosis. The exudates on the retinal veins are round, oval or stripe-shaped, with woolly, ill-defined outlines, and occur in the peripheral regions of the fundus not nearer than 2 or 3 disc diameters from the disc. Two to 25 exudates may be present at a time in one fundus. Repeated observations reveal that they are transient; some exudates disappear as others appear. After 3 to 23 months the exudates either disappear completely or persist. In the arrested type, narrow, sharply defined white lines along the blood column, or round or oval white spots remain stationary and are permanent. Pathological studies and the frequent association of multiple sclerosis with periphlebitis support Haarr's theory that the same, but unknown, factor gives rise both to periphlebitis and to the development of chronic sclerotic plaques in the central nervous system. It would seem that the nervous system plaques are of the same type as those seem in the retina. One practical conclusion is that any drug regarded as effective in the treatment of multiple sclerosis should be expected also to influence active periphlebitis favorably. Active periphlebitis, thus, may serve as an indicator of the effectiveness of the treatment.

Subhyaloid Hemorrhage.—Subhyaloid hemorrhage occurs infrequently in association with intracranial subarachnoid hemorrhage but may be a helpful sign in the diagnosis of cerebral disease. Cordes [55] briefly reviews the recent literature and reports two cases, one due to hypertension, and one due to bleeding from a metastatic tumor of the brain. The subhyaloid hemorrhages were bilateral in both cases.

Pulseless Disease.—Pulseless disease is an unusual syndrome, first described in 1908 by Takayasu. All reported cases were in the Japanese literature until Aggeler, Lucia, and Thompson, in 1941, described a condition which, in retrospect, can be regarded as pulseless disease. The first non-Japanese report of a case of a condition specifically diagnosed as pulseless disease was by Caccamise and Whitman in 1952. Caccamise and Okuda [56] now call the attention of ophthalmologists to the syndrome. More cases will be encountered as familiarity with the entity increases.

Briefly, the cardinal manifestations are absence of pulsations of the radial arteries, absence of detectable blood pressure in the upper extremities, and ocular findings of peripapillary arteriovenous anastomoses and complicated cataracts. In advanced cases the entire retinal vascular tree is converted into simple peripapillary arteriovenous loop anastomoses. The essential lesion is a progressive occlusion of the subclavian and carotid arteries, due presumably to panarteritis. Depending upon the

impairment of the cerebral arterial supply, there will occur diverse neurological manifestations, such as syncope, hemiplegia, hemianesthesia, aphasia, and convulsions.

Lawson [57] reports the case of a woman, age 45, with pulseless disease who developed right hemiplegia, hemianesthesia, and bilateral blindness.

Intracranial Aneurysms

Pathogenesis of Cranial Nerve Palsies.—Hyland and Barnett [58] found that the pathological mechanisms causing palsies of the second, third, and sixth cranial nerves in 39 cases of intracranial aneurysms with autopsy comprised two groups. In the first group (20 cases) transient pareses were due probably to compression of the nerve by the gradually enlarging, but unruptured, aneurysm. Aneurysmal leaking or rupture, however, caused hemorrhage into the nerve. The ensuing fibrous tissue proliferation caused the nerve to adhere to the sac, leading to irreversible nerve damage and permanent nerve palsy. In the second group (19 cases) the nerve palsies were usually bilateral, occurred during the terminal two weeks of life, and resulted from severe intracranial hemorrhage. Four mechanisms were found: (*a*) midbrain hemorrhages in the region of the oculomotor nuclei due to increased intracranial pressure; (*b*) kinking and compression of the nerve due to displacement of the posterior cerebral artery, resulting, in turn, from displacement of the brain stem by hemorrhage; (*c*) compression of the third nerve by hippocampal uncus herniation, and (*d*) stretching or compression of the brain stem due to sudden intracerebral and intraventricular hemorrhage.

Bilateral Aneurysms.—King, Slade, and Campoy [59] report six cases of bilateral intracranial aneurysm which were revealed by performing bilateral carotid angiography in 34 of 121 aneurysm suspects. The authors emphasize the advisability of investigating the carotid circulation on both sides before performing surgical ligations. Perhaps some unsatisfactory surgical results are due to an undetected aneurysm on the contralateral side. It it interesting that Blane reported the first case of intracranial aneurysm in English in 1800 and that this was bilateral.

Carotid Artery—Cavernous Sinus Fistula

Tonometer Sign.—Boyes and Ralph [60] describe a method of detecting minimal pulsation of the eyeball when digital and visual methods reveal no pulsation. When determining the intraocular pressure in the homolateral eye, the authors observed that the tonometer pointer described to-and-fro movements, synchronous with the carotid arterial pulsations, over an arc of six to eight divisions on the scale. Pulsation of the globe could not be observed or palpated. Homolateral glaucoma was found in two cases of spontaneous carotid artery-cavernous sinus fistula. Spontaneous thrombosis effected a cure, with normalization of the intraocular pressure.

Visual Results.—Elliot [61] records 10 cases of carotid artery-cavernous sinus fistula and discusses in particular the visual results obtained. A carotid artery-cavernous sinus communication may produce a reversal of blood flow in the ophthalmic artery, with a consequent drop in the pressure in the retinal arteries. An increase in venous pressure also occurs, and this combination probably explains the visual impairment which frequently occurs. Retinal anemia is due to retrograde flow through the ophthalmic artery into a patent carotid-cavernous communication. Treatment should be directed toward three signs: proptosis, visual impairment,

and subjective head noise. Spontaneous thrombosis may occur and be associated with preservation of normal vision. The operation of choice is ligation of the cervical portion of the internal carotid artery and intracranial ligation of the ophthalmic artery to prevent the retinal anemia.

Pulsating Exophthalmos.—Bonnet [62] describes in detail the pathological physiology of traumatic pulsating exophthalmos. In fracture of the sphenoid bone the adjacent internal carotid artery is torn. Three clinical pictures are possible. In the first, the carotid artery communicates with the fractured sphenoid sinus and leads to fatal epistaxis. In the second, a carotid artery-cavenous sinus fistula results, producing subjective head noises, venous congestion and chemosis of the bulbar conjunctiva, pulsating exophthalmos, palpable thrill over the eyeball, retinal cyanosis and hemorrhages, reduction in retinal arteriolar pressure, glaucoma, muscle palsies, and, occasionally, optic nerve injury. Vertigo and deafness are due probably to venous congestion in the internal ear; cough is due to pressure on the vagus nerve. In the third type, a diffuse mass of extradural blood compresses the cavernous sinus, acting as a tumor in the middle cranial fossa. The thrill is absent; head noises are less noticeable, and the exophthalmos is not always pulsatile. The exophthalmos may be bilateral or may be contralateral to the fistula; therefore, arteriography should be done before operative ligations are performed.

MULTIPLE CRANIAL NERVE PALSIES

Cavernous Sinus Syndrome.—Jefferson [63] describes the ocular manifestations of lesions involving the cavernous sinus, his opinions being based upon 112 lesions personally encountered and pathologically verified at operation or necropsy. The reader is reminded that proptosis in septic cavernous thrombosis is due to cellulitis and thrombosis of the orbital veins, rather than to back pressure from a blocked sinus. The sinus can be blocked by a large tumor or aneurysm without producing signs of orbital or retinal venous stasis; if such signs do occur, they are caused by thrombosis extending into the orbital veins.

Traumatic Ophthalmoplegia (five cases): Although fractures of the cranial base frequently cross under the cavernous sinus, injury to the sinus is uncommon. Most ocular palsies appearing after head injuries involve individual muscles; these are due to intraorbital contusion and are not related to cavernous sinus injury. The most certain sign of sinus injury is the involvement of more than one of the oculomotor nerves, preferably all of them, plus the trigeminal nerve.

Traumatic Carotid-Cavernous Fistula (17 cases): It is difficult to determine whether a fistula develops at the instant of the head injury or subsequently. The time of onset of the telltale subjective bruit may be obscured by the patient's coma. The objective bruit is not commonly found early because injured heads are not routinely auscultated. The arterial rupture is most likely delayed from a few hours to several days. The one constant feature is the bruit. Muscle palsies are common and are probably due to circulatory disturbances in the orbit. Trigeminal anesthesia is less common. Pulsating exophthalmos is uncommon or may be scarcely perceptible.

Intracavernous Saccular Aneurysm (29 cases): Most of these aneurysms, including those which spontaneously rupture to form fistulae, occur in women over 50, whereas aneurysms of the circle of Willis are commoner in persons under 40. Jefferson emphasizes that aneurysms can cause severe pain and yet not destroy

nerve bundles; conduction recovers and numbness disappears, leaving no discernible trigeminal nerve damage. This is in striking contrast to the persistent pain occurring when the ganglion is invaded by tumor. Intact corneal sensation is an absolute criterion of normality of the trigeminal nerve. The ophthalmoplegias tend to recover, but incompletely. A common permanent result is miosis and narrowing of the palpebral aperture on the affected side.

Tumors Involving the Cavernous Sinus (52 cases): Primary tumors are rare. Secondary tumors, by extension or metastasis, are in the majority. The author's series included 23 nasopharyngeal malignant tumors; 11 invasive pituitary tumors; 8 carcinomatous metastases from the breast, lung, prostate, stomach, and face; 2 adamantinomas; 3 meningiomas of the sinus or Gasserian sheath; 4 neurinomas of the Gasserian ganglion, and 1 chordoma.

Invasion by Pituitary Tumors: About 5% of pituitary tumors break through their capsules into the cavernous sinus. Oculomotor palsies are not reliable signs of such invasion, since they can be caused also by compression of the third and fourth nerves against the interclinoid ligament. Histological verification is the only reliable proof of invasion. Clinically these cases are easily mistaken for saccular aneurysms, since they often present abrupt onset of pain, oculomotor palsies, normal acuity and visual fields, normal menstruation, normal sugar tolerance curves, and normal or equivocal x-rays of the skull.

Malignant Invasion: In the literature of 1900 to 1930 were numerous reports of primary tumors, called "endotheliomas," of the cavernous sinus and Gasserian ganglion. Many of the patients, however, developed enlarged cervical lymph nodes and died within two years after the cranial operation. More recent knowledge supports the conclusion that these earlier tumors were not primary, but were extensions of malignant nasopharyngeal neoplasms, which often have an endotheliomatous appearance; furthermore, meningiomas do not metastasize to the cervical lymph nodes.

Monocular blindness (in 12 cases) and trigeminal pain and anesthesia (in 37 cases) are much commoner in cavernous sinus tumors than in aneurysms. Since the optic nerve is outside the sinus, blindness cannot be included as part of the cavernous sinus syndrome; yet the proximity of the nerve to the anterior end of the sinus makes its involvement probable if the sinus is packed with tumor. Compression occurs either by the sinus bulging against the nerve and kinking it or by the extracavernous infiltration of the tumor into the sphenoid or posterior ethmoid sinuses. In all cases of monocular blindness the first trigeminal division was also damaged; in some the second and third divisions were also involved. In none of the five cases of isolated anesthesia of the mandibular division alone was the optic nerve affected.

Monaural deafness is common but is due usually to blockage of the Eustachian tube; if it were due to nerve involvement, the facial nerve would also be paralyzed but this is rare.

Unilateral palsy of cranial nerves II, III, IV, V, VI, X, XI, and XII is most frequently due to intracranial or extracranial infiltration by a nasopharyngeal tumor. The nerve groups may be of many or few, and in any order.

Invasion of the sinus can occur by spread of the nasopharyngeal tumor up along the internal carotid artery sheath to enter the intracranial cavity through the foramen lacerum; from here it grows into the posterior part and root of the Gasserian

ganglion and thence into the cavernous sinus. This explains why trigeminal affection is the commonest and the most certain of the early signs of intracranial invasion. Purely extracranial invasion, involving the mandibular division alone, occurred in five cases. Another method of spread is by infiltration anteriorly into the pterygomaxillary (pterygopalatine) fossa, or superiorly into the sphenoid sinus and thence into the cavernous sinus.

It is evident that syndrome of the sphenoidal fissure and orbital apex may be an alias for lesions of the anterior end of the cavernous sinus.

Multiple Myelomatosis.—A rare cause of multiple cranial nerve palsies is multiple myelomatosis. Clarke [64] reports the case of a woman, age 61, who had involvement of the right optic, trigeminal, and abducens nerves and of both auditory nerves. X-rays demonstrated extensive destruction of the bones of the skull base. Biopsy of a nasopharyngeal mass revealed plasma cell myeloma. The neoplasm arises from bone; the overlying dura usually remains intact, and the cranial nerves are affected either by local distortion or by direct destruction due to tumor invasion of the cavernous sinus or cranial foramina. Multiple myelomatosis should be suspected in destructive lesions of the skull base, such as nasopharyngeal cancer, extrasellar extension of pituitary tumor, and chordoma. Final diagnosis requires biopsy studies or demonstration of myelomatosis elsewhere in the body.

Carcinomatous Neuropathy.—One of the most interesting conditions gaining recognition in the past few years is carcinomatous neuropathy, in which neurological syndromes are associated with systemic carcinoma in the absence of metastatic deposits in the nervous system. Involvement of the cranial nerves innervating the ocular structures may be the earliest manifestation or may develop during the course of the disease. For this reason, ophthalmologists should become acquainted with this syndrome. Sensory or motor neuropathy, cerebellar degeneration, and myopathy comprise the neurological manifestations. Older books refer to the condition as polyneuritis due to carcinomatous cachexia.

Hanson, Russell, and Wilkinson [65] report 19 cases, including 11 with necropsy studies, and discuss the literature. Carcinoma of the lung was found in 17 patients, carcinoma of the breast in 1, and carcinoma of the ovary in 1. Diplopia, ptosis, and pupillary changes were observed in several of the patients. Surprisingly, neurological symptoms preceded those due to the carcinoma, or preceded the diagnosis of the carcinoma, in 15 of the 19 cases. Recognition of the clinical picture of carcinomatous neuropathy led to the discovery of the carcinoma in 10 of the cases. The authors emphasize that months or years may elapse before the causal cancer can be detected. Necropsy fails to reveal any metastatic lesions to account for the neurological signs. It has been suggested that a metabolic disorder may be a factor in the syndrome.

Heathfield and Williams [66] report five cases of carcinomatous neuropathy and myopathy, all associated with carcinoma of the lung. They also stress that there may be a long time interval between the onset of the peripheral neuropathy and the first symptom of the lung carcinoma, and they believe that the primary sensory neuropathy is so characteristic of this syndrome that bronchoscopy should be performed if the chest x-rays are negative.

HEAD INJURIES

Oculocardiac Reflex.—In cases of head injury the detection of a resulting intracranial hematoma is important. A valuable sign, considered almost pathognomonic

of intracranial hematoma, is a slowing of the pulse rate, caused by increased intracranial pressure. However, trauma to the eyeball or orbit can decrease the pulse rate even though there is no intracranial hematoma. This is due to the oculocardiac reflex, a phenomenon to be considered in all cases of head injury.

Störtebecker [67] reports the case of a man, age 25, who was struck with a fist and fell to the pavement, striking his occiput; he was unconscious a few moments. Intracranial hematoma was diagnosed. Neurological examination was negative, but there was a subconjunctival hematoma of the left eye and slight dilatation of the left pupil, which reacted sluggishly to light. Skull x-rays revealed no fracture. Four hours after the accident the pulse rate was 36 per minute, the blood pressure was 120/80, and respiratory rate was 20 per minute. The patient was mentally clear, with no retrograde amnesia. There was considerable edema of the left eyelids and slight edema of the left retina. Intraocular pressure was normal and equal in the two eyes. Electrocardiograms revealed only a slight slowing of the pulse rate when moderate pressure was exerted on the healthy right eye, but mild pressure on the left eye provoked extreme bradycardia. The trauma seemed to have sensitized the left eye to the oculocardiac reflex. Four days after the accident the pulse rate was 40. One and a half years later the neurological and ocular examinations were normal. The pulse rate was 60, and pressure on either eyeball slowed the rate to 50 per minute.

The nerve pathway for the reflex is considered to course over the trigeminal nerve to the pons, where the reflex center is situated; from here the efferent fibers pass through the vagus nerve to the heart. Digital compression of the eyeball through the closed lids elicits the reflex and is used therapeutically in paroxysmal tachycardia. The reflex can also be elicited by subconjunctival injection of saline solution and by periocular edema, as in congestive glaucoma. It has been observed after enucleation of the eyeball, with subsequent intraorbital hematoma. Severe oculocardiac reflex can cause the heart to come to a standstill in diastole.

The oculocardiac reflex can be abolished by retroganglionic section of the trigeminal sensory root and by atropine administration and is rapidly and efficaciously controlled by a retrobulbar injection of procaine and epinephrine. It may be necessary to evacuate an intraorbital hematoma to control the reflex.

Orbitocranial Penetrating Injuries.—Platt [68] and Kjer [69] remind us that a penetrating wound of the orbit, even though the external lesion is small, is serious, especially if the globe is intact, and should always be regarded as having perforated the orbital walls and injured the brain. Neurological signs may be delayed in onset or may escape notice unless specifically searched for. They advise immediate hospitalization, neurological examination, and administration of tetanus antitoxin and antibiotics. X-rays should be taken, but they frequently do not show fractures which are revealed at operation. Spinal fluid examination, air studies, arteriography, and craniotomy can be employed as advised by the neurosurgeon.

Bitemporal Hemianopia.—Jaffe [70] reports a case of bitemporal hemianopia occurring in a 23-year-old man who sustained a basal skull fracture extending through the right greater wing of the sphenoid bone. Since it is not stated how soon after the accident the field studies were determined, it cannot be deduced whether the chiasmal fibers were torn at the instant of the accident or whether they suffered discontinuity later, due to interruption of the blood supply.

Conjugate Gaze Discomfort.—Savitsky and Madonick [71] report concerning the clinical significance of discomfort with conjugate gaze studied in 2,604 cases of head injury. Among these were 5.3% (138 cases) in which there were no palsies of gaze or visual field defects but in which the patients complained of discomfort with conjugate gaze. The authors feel that this is a sign of organic injury to the brain and may be the only objective evidence of injury, and that it is probably due to involvement of the supranuclear vestibulo-ocular mechanism within the brain stem.

X-RAYS IN NEURO-OPHTHALMIC DIAGNOSIS

Cerebral Calcification.—Walsh and Murray [85] review the conditions of neuro-ophthalmic interest in which calcium deposits in the brain are revealed in the x-rays. These include calcification occurring (*a*) physiologically in the pineal gland, petrosphenoidal ligament, and choroidal plexuses of the lateral ventricles; (*b*) in neoplasms, such as craniopharyngioma, dermoid cysts, meningiomas, gliomas, and angiomatosis; (*c*) in hemorrhages and subdural hematomas of long-standing; (*d*) in the meninges following inflammation; (*e*) in parasitic lesions, such as toxoplasmosis, echinococcosis, and trichiniasis, and (*f*) in the intracranial arteries.

Cerebral Angiography.—Unilateral or bilateral visual field defects, in the absence of other ocular, neurological, or medical signs, are due frequently to intracranial lesions which are not revealed by ordinary x-ray films of the skull. The value of angiography in the recognition of numerous lesions in the region of the optic chiasm is emphasized by Joy, Ecker, and Reimenschneider [72] in a paper describing the normal anatomy of this region, the technique of angiography, the appearance of the arterial pattern in normal persons and in those harboring presellar and suprasellar lesions, and the complications that may occur. The numerous details in the illustrations and in the text cannot be summarized but should be studied by the interested ophthalmologist. The authors state that the degree of displacement of the arteries does not necessarily indicate the size of the tumor, and that angiography does not always indicate the pathological nature of the lesion. They feel that serious complications, though rare, are worth risking in view of the valuable information obtained by angiography.

Monographs.—The book by Epstein and Davidoff [73] is a valuable reference work, containing considerable information for the neuro-ophthalmologist. The value of laminography in the diagnosis of lesions involving the base of the skull is presented in a monograph by Fischgold, David, and Brégeat.[74]

SURGICAL PROCEDURES

Transorbital Lobotomy.—Čavka [75] reports anisocoria, conjugate deviations, and ocular muscle paralyses occurring in the immediate postoperative period in 10 cases of transorbital prefrontal lobotomy. In all cases the eye manifestations cleared in a short time.

Craniostenosis.—The craniostenoses comprise the diverse types of craniofacial deformities resulting from premature fusion of the cranial sutures. The varied neurological and ophthalmological manifestations, attributable in general to bony structural malformations and to increased intracranial pressure, have been recognized for many years. More recently the advances in neurosurgical techniques have

renewed the interest in this condition, as exemplified in the excellent reviews and case reports by Anderson and Woodhall,[76] Howell,[77] and Koziak.[78]

The most serious ocular sign is optic atrophy, due usually to papilledema secondary to increased intracranial pressure. Kinking or compression of the optic nerve may also be a factor. The authors emphasize the urgency of recognizing the skull deformity early so that surgical intervention can be instituted during the first or second year of the infant's life. Operation consists of linear craniectomy along the prematurely fused cranial sutures; subsequent closure is prevented by placing a sheet of polyethylene film or tantalum foil along the edges of the bony defects.

Anderson and Woodhall [76] advise that the ophthalmologist be familiar with this subject so that he will be alert to recognize the skull deformity within the first year of the infant's life. Only in this way can operation be done in time to prevent irreparable blindness.

In cases with both papilledema and excessive exophthalmos, Howell [77] recommends that the intracranial pressure be normalized first; after this is accomplished, the orbit and optic canals can be unroofed. If deroofing is done simultaneously with, or too soon after, the cranial operation, there may develop increased proptosis, or even evulsion of the globe, due to surgical edema.

Koziak [78] stresses the value of x-ray studies of the skull in investigating loss of vision in order to detect evidence of craniostenosis.

Transcranial and Orbital Approaches to Orbital Tumors.—One of the most interesting and most challenging problems in neuro-ophthalmology concerns the surgical excision of tumors situated in the posterior portion of the orbit. There is considerable disagreement among surgeons as to whether the transcranial or the orbital approach is the safest, and most therapeutically effective and functionally satisfactory method.

Love and Dodge [79] discuss the indications, advantages, and technique of the transcranial approach. From the experience gained in 108 cases, they believe that the neurosurgical approach is safe and practicable and that it offers the patient the fullest chance of obtaining intact vision. Berke [80] describes the anatomy and technique of his method of orbitotomy, which he refers to as a modified Krönlein operation, and states his views on the indications, contraindications, advantages, and disadvantages of the orbital approach. In general he prefers the orbitotomy, even in cases of glioma of the optic nerve which has extended intracranially. Both papers are excellent and should be studied by surgeons interested in this fascinating subject.

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Correspondence

LINT IN THE ANTERIOR CHAMBER AFTER SURGERY

To the Editor:—Referring to the recent report by R. J. Brockhurst (Cotton Fibrils in the Anterior Chamber After Surgery, A. M. A. Arch. Ophth. **52**:121-124 [July] 1954), I wish to call attention to two additional possible sources of contamination by reporting three cases in my own practice of cotton fibrils retained in the anterior chamber. The source of contamination appears to have been established by trial and error.

The first case was an uncomplicated cataract extraction, in which, however, eventual slit-lamp examination revealed several short, white, apparently cotton, fibrils lying on the iris and extending across the pupillary border on the vitreous surface. In the belief that the source of contamination was the cotton-tipped applicators employed for sponging, the use of cotton sponges was discontinued and replaced by fine-pore, cellulose sponges.

That cotton sponges were not the source of lint was evident when a second case, also one of cataract extraction, occurred after an interval of several months. It being considered possible that the lint was a contaminant of the saline solution used to irrigate and re-form the anterior chamber prior to tying the corneal-scleral sutures, all solutions on the operating tray from that time on were either commercial triple distilled water or commercial saline prepared for intravenous use. Here it should be pointed out that many general hospitals prepare their own saline and distilled water solutions. Examination of several operating-room solution specimens in test tube containers by means of the slit-lamp beam showed one batch to contain small lint fibrils. Obviously, solutions prepared by hospital personnel in the absence of adequate controls cannot be accepted without question.

However, the occurrence of a third case demonstrated that saline solution itself was not the source of contamination. The third case was one of proved sympathetic ophthalmia in which acute glaucoma developed secondary to complete posterior synechia forming unobserved in the dilated pupil. An iridectomy was done and the anterior chamber was irrigated free of slight bleeding. Postoperative slit-lamp examination demonstrated four small pieces of lint retained in the anterior chamber.

Further consideration of possible sources suggested that lint might be transferred into the medicine glasses and other solution containers used on the operating tray by the cotton or linen cloth in which they had been wrapped for autoclaving. Accordingly, henceforth all solution containers were thoroughly rinsed with commercial saline before being filled for use. No further cases have occurred.

In our cases there was no evidence of ocular morbidity resulting from lint introduced into the eye at the time of surgery. After a period of some months (in the glaucoma case it is now 18 months since surgery) the fibrils gradually acquired a mild pigment deposition. Obviously, restraint in intraocular irrigation would do much to minimize the introduction of cotton lint into the anterior chamber during surgery.

In summary, in addition to lint circulating in the operating-room air, as reported by Vail (Vail, D.: Lint in the Anterior Chamber Following Intraocular Surgery, *Am. J. Ophth.* **34**:1533-1538, 1951), and to cotton fibrils from short-staple cotton sponges, as reported by Brockhurst, attention is called to two additional possible sources of contamination: (1) improperly prepared saline solution, and (2) solution containers lint-contaminated by the cloth in which they were wrapped for sterilization.

Robert E. Shoemaker, M.D.
1248 Hamilton St., Allentown, Pa.

Obituaries

PROF. MAXIMILIAN SALZMANN
1862-1954

Prof. Maximilian Salzmann died suddenly at his home in Graz, Austria, on April 17, 1954. In his passing, ophthalmology lost an eminent scientist, a masterful teacher and writer, and a beloved person.

Born in Vienna, in 1862, Professor Salzmann was graduated from the university there as a Doctor of Medical Science in 1887. A year later he became an assistant

Salzmann

to Prof. Ernst Fuchs, whose renown attracted ophthalmologists from all over the world. After serving as Chief Instructor, and subsequently as Assistant Professor of Ophthalmology under Professor Fuchs at the University of Vienna, Dr. Salzmann was in 1911 named Professor of Ophthalmology at the University of Graz, Austria. It was in this position that he spent his remaining and productive years.

He was best known in this country because of his peerless book "The Anatomy and Histology of the Human Eyeball in the Normal State, Its Development, and Senescence." This book has been widely employed by English-speaking ophthalmologists because of the translation made by the late Dr. E. V. L. Brown. He made numerous original contributions to the histology and pathology of the eye.

He had an extraordinary knowledge of mathematics, and he applied this in ophthalmology in the field of geometric optics, in which he made noteworthy contributions.

Although no generally known, he was actually the father of gonioscopy because of his pioneer contributions on this subject, entitled "Die Ophthalmoskopie der Kammerbucht."[1] By employing the indirect ophthalmoscope, he devised the first successful method of viewing the angle of the anterior chamber.

Professor Salzmann was also an excellent painter. When, in 1890, he revised Jaeger's "Ophthalmological Atlas," he amplified it with his own drawings. He made all of the drawings which illustrate his classic book on the anatomy and histology of the human eye, previously referred to. It was his practice to illustrate richly all of his papers with his own masterful drawings. As a token of exceptional esteem, Professor Fuchs designated him to revise his textbook, and Professor Salzmann supplemented the text with his fundus drawings.

It is ironical that Professor Salzmann lost practically all of his vision during the last years of his life because of macular changes associated with high myopia. He described the gradual development of these changes subjectively in his last contribution, in 1953.[2] His sagacious intellect, however, remained astute to the end of his magnificent 92 years.

Those of us who had the rare privilege of visiting Professor Salzmann in Graz know full well his charming hospitality, his true devotion and consecration to ophthalmology, his contagious enthusiasm for teaching, and his unstinted gift of his time. We have lost a truly great ophthalmologist.

A. B. Reese, M.D.

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2. Salzmann, M.: Über Rückbildung (Schwund) von cilioretinalen Arterien, von Graefes Arch. Ophth. **153**:451-458, 1952-1953.

News and Comment

EDITED BY DR. W. L. BENEDICT

GENERAL NEWS

Call for Papers.—The 1955 Meeting of the Section on Ophthalmology will be held in Atlantic City, N. J., June 6-10, 1955, simultaneously with that of the Association for Research in Ophthalmology.

Anyone wishing to present a paper before the Section is urged to communicate with Dr. Harold G. Scheie as soon as possible. A title and abstract, of not less than 30 or more than 150 words, must be in his hands by Jan. 1, 1955. Anyone wishing to present a paper before the Association for Research should contact Dr. Lorand V. Johnson as soon as possible.

Members are reminded that their contributions to the Knapp Fund are now due and payable to Dr. Parker Heath, 243 Charles St., Boston. A $10.00 contribution entitles you to a volume of the 1954 *Transactions*. Contributions in excess of $10.00 are invited.

HAROLD G. SCHEIE, Secretary
Section on Ophthalmology
313 S. 17th St.
Philadelphia 3

LORAND V. JOHNSON, Secretary
Association for Research in Ophthalmology
10515 Carnegie Ave.
Cleveland 6

Postgraduate Course in Ophthalmology, Walter Reed Army Medical Center.—A short postgraduate course in ophthalmology will be held at Walter Reed Army Medical Center on Feb. 2, 3, and 4, 1955. The following civilian guest lecturers are supplemented by military ophthalmologists on the program: Prof. Marc Amsler, of Zurich, Switzerland; Drs. J. S. Friedenwald, W. F. Hughes Jr., P. C. Kronfeld, and L. E. Zimmerman.

The meeting is open to military and civilian ophthalmologists, with no fee. Applications for military personnel should be processed through channels in accordance with SO Circular No. 43, dated May 18, 1954. Civilians who wish to attend should apply to the Commanding General, Walter Reed Army Medical Center, Washington 12, D. C.; Attention: Col. J. H. King Jr., Course Director in Ophthalmology.

University of Toronto Course in Eye, Ear, Nose and Throat Surgery.—The Faculty of Medicine of the University of Toronto offers a combined refresher course in Eye, Ear, Nose, and Throat Surgery from April 11 to 15, 1955. The instruction will consist of didactic lectures and surgical demonstrations emphasizing the office practice of ophthalmology and otolaryngology.

The guest surgeons will be Dr. Alson E. Braley, Professor of Ophthalmology, University of Iowa, Iowa City; Dr. Frank B. Walsh, Associate Professor of Ophthalmology, The Johns Hopkins Hospital, Baltimore; Dr. Edmund P. Fowler Jr., Professor of Otolaryngology, Columbia University College of Physicians and Surgeons, New York, and Dr. Dean M. Lierle, Professor of Otolaryngology and Maxillofacial Surgery, University of Iowa, Iowa City.

The staff of the Departments of Ophthalmology and Otolaryngology in the University will contribute to the course. The course will be held for a minimum of 10 and a maximum of 30 students. The fee will be $100.00, payable to the Chief Accountant, Simcoe Hall, University of Toronto. Applications should be made to the Dean of the Faculty of Medicine not later than Feb. 15, 1955.

Research Study Club of Los Angeles Mid-Winter Clinical Convention.—The Research Study Club of Los Angeles announces its 24th Annual Mid-Winter Clinical Convention in Ophthalmology and Otolaryngology, Jan. 17 through Jan. 28, 1955.

For the Ear, Nose, and Throat program, the guest lecturers will include Dr. Theodore E. Walsh, Professor and Head of the Department of Otolaryngology, Washington University School of Medicine, St. Louis, and Dr. John J. Conley, Chief of the Head and Neck Service, St. Vincent's Hospital, New York, and Clinical Professor of Otolaryngology, New York University. Also serving on our program with didactic lectures will be Drs. Kenneth C. Brandenbury, of Long Beach; J. C. Almy Harding, of San Diego, and Paul J. Moses, of San Francisco. Instruction courses in otolaryngology will be provided by Drs. E. R. V. Anderson, Norman Jesberg, Harold Owens, and Manuel R. Wexler, all of Los Angeles, and Leo Shahinian, of San Francisco.

The guest lecturers for the eye program will be Dr. Edmund B. Spaeth and Dr. Irving H. Leopold, both from the University of Pennsylvania Graduate School of Ophthalmology.

Instruction courses in ophthalmology will be given by Mrs. Helenor Campbell Wilder Foerster and Dr. Robert H. Shaffer, both of San Francisco.

The first week will be devoted to the ear, nose, and throat—from Monday to Saturday, Jan. 17 through Jan. 22. The eye week will cover Monday to Friday, Jan. 24 through Jan. 28.

The American Laryngological, Rhinological and Otological Society, Western Section, will hold its annual meeting at The Town House immediately preceding this Convention, Saturday and Sunday, Jan. 15 and 16. On Saturday afternoon the scientific session is open to members and all interested otolaryngologists. Saturday evening there will be a dinner meeting for members of the Triologic Society only. Sunday morning, the second scientific session is open to all interested.

For more complete information, write to The Research Study Club of Los Angeles, 1930 Wilshire Blvd., Suite 1411, Los Angeles 57.

PERSONAL NEWS

Dr. Otto Barkan Awarded the Prize in Ophthalmology for 1954.—Dr. Edwin B. Dunphy, Boston, stated: "Before presenting the Prize in Ophthalmology for this year, I want to say a few words about it and tell you something about the philosophy which lies behind it. The Prize in Ophthalmology differs from many other awards. It is given to a member of this section not for the best paper on the program nor for having made some world-shaking discovery but, rather, for his general contributions to our science over a period of years. The recipient is chosen by the executive committee of the section, and therefore I, as the current chairman of that body, have the duty to make the presentation. This year the committee has selected Dr. Otto Barkan, of San Francisco."

SOCIETY NEWS

Georgia Society of Ophthalmology and Otolaryngology.—The Georgia Society of Ophthalmology and Otolaryngology will meet March 11-12, 1955, at the General Oglethorpe Hotel, Savannah, Ga.

The speakers will be Dr. Francis H. Adler, Philadelphia; Dr. J. W. McCall, Cleveland; Dr. J. A. Hilger, St. Paul; Dr. Walter H. Fink, Minneapolis; Dr. James H. Allen, New Orleans, and Dr. P. E. Ireland, Toronto, Canada.

Société française d'ophtalmologie.—The 61st meeting of the Society was held in Paris, May 23 through 27, 1954. This is usually very conspicuously an international gathering, with many members from overseas. This year, probably on

account of the São Paulo Pan-American Congress in June and the XVII International Congress of Montreal and New York in September, very few crossed the ocean. Busacca, from São Paulo, and Gardiner, from New York, were the only ones from the Western Hemisphere. The British were also less numerous, but there were strong contingents from Belgium and Switzerland.

As usual, the Société published a book a few months before the meeting. This year it was "Biology of the Lens" ("Biologie du cristallin"), written by Prof. J. M. Nordmann, of Strasbourg. It was sent free to all members of the French Society, and nonmembers can purchase it by applying to the treasurer of the Society, Dr. Jean Charpentier, 28 rue Vignon, Paris 9, or to the publisher, Masson & Cie, 120 Boulevard Saint Germain, Paris 6e (730 pages, with 169 figures; price, 4,500 francs).

This very comprehensive work can hardly be condensed into a few lines. The anatomy, physiology, chemistry, and pathology of the lens are fully studied, and the author gives a large amount of interesting material from his personal researches. On Tuesday, May 25, Nordmann gave an excellent presentation, and this was followed by papers dealing with similar problems and by a discussion, in which a dozen members took part. The surgical problems of cataract were not dealt with—only the biology of the lens and the fascinating problem of why it clouds. No answer was given to this question, although it was evident that for Nordmann, as well as others, the metabolism of the glucides was probably the key to the problem.

On Monday, May 24, the papers were on neuro-ophthalmology. Čavka (Sarajevo) had examined patients undergoing prefrontal leucotomy and frontal topectomy for schizophrenia and reported on ocular and neurological signs observed. Larmande and Sutter (Algiers) read a paper on reading difficulties. These authors found between 4 and 10% of school children affected. Although the vision is normal, the dyslexia is apt to mislead the examiner and give too low a measure of visual acuity. Blagojević and Milenković (Belgrade) reported a case of the Foster Kennedy syndrome in a patient with pituitary tumor. P. Bonnet and I. Bonnet (Lyons) read a paper on the ocular symptoms of cerebral angiomatosis. Offret and Massin (Paris) read a paper on intracranial aneurysms with ocular symptoms and stated that it was not always possible to deal directly with the lesion surgically, the risks being too great, and that treatment was often limited to palliative measures. Thomas, Cordier, and Algan (Nancy) reported that they had had better results in optochiasmatic arachnoiditis when cortisone was added to the usual operative and antibiotic treatments. Brégeat, Fischgold, and David said that they were very well satisfied with the information given by tomography in chiasmatic gliomas. Dubois-Poulsen and Magis (Paris) observed in three cases of occipital tumor a scotoma on the vertical midline. Dollfus and co-workers (Paris) reported on a case of Devic's disease in which vitamins, antibiotics, and corticotropin improved the condition rapidly, but without a complete cure of the motor and visual symptoms. Man (Paris) read a paper on the possibility of a pseudo von Graefe sign during the period of recovery of an oculomotor paralysis.

On Wednesday, May 26, the papers were on the lens. Dekking (Groningen) demonstrated an instrument for measuring the opacity of the cornea and the lens. Dufour and co-workers (Lausanne) observed 14 patients with oligophrenia and congenital cataract. Babel (Geneva) reported the case of a man aged 50 who had been affected since childhood with tetany and in whom, late in life, there developed a cataract due to that disease. Viallefont and Boudet (Montpellier) read a paper on the removal of cataract in eyes previously affected with tuberculous uveitis. With proper care, favorable results can be obtained. Guillaumat and Girard (Paris) reported on 100 cases of congenital cataract treated surgically. The end-results were often disappointing. The worst cases were those of bilateral total hard cataracts. The prognosis was also poor when there was nystagmus or microphthalmos and when the pupil dilated poorly. Calmettes, Deodati, and Almerić (Toulouse) were very well satisfied with the use of the Harrington erysiphake. Sedán and Farnarier

(Marseilles) read a paper on what should be done when a patient has both cataract and a detached retina. Paufique (Lyons) reported on his experience with the Ridley operation. Results were, on the whole, satisfactory in well-chosen cases, but complications, in particular iridocyclitis and dislocation of the lens, were frequent. Baron (Nantes) has tried, after cataract operation, to place a plastic prosthesis in the anterior chamber, and in corneal grafting he uses a plastic transplant. Rougier (Lyons) compared the visual results in cases of unilateral lens extraction in 60 cases corrected with contact lenses and in 25 cases of the Ridley operation. Binocular vision was usual in the Ridley operation and much less the result with the contact lens.

Sunday, May 23, was devoted to "free papers." Charamis (Athens) reported four cases of ocular injury by shot. In one case the foreign body had gone right through the eye, and the final vision had been good. In two cases there had been only a contusion, with retinal edema and tear; in both cases electrocoagulation was successfully used. In the fourth case the optic nerve was sectioned near the apex. Zanén, Meunier, and Piraux (Brussels) measured the actual concentration of oxygen in the incubators for premature babies. They found great variations, depending on the manufacturers. Retinopathy occurred much more frequently when the concentration was high. Voisin and Lombard (Paris) reported a case of pseudoxanthoma with macular lesions but no angioid streaks. The authors asked whether obstruction of the arterioles was not an essential cause of the ocular lesions. Ducluzaux (Versailles) found that in anisometropia facial asymmetry and nasal lesions are frequent. They observed that with surgical treatment of the nasal disturbance the anisometropia would slowly decrease. The pathogenesis is obscure. Salgado-Gomez (Barcelona) reported good results with scleral resection in retinal detachment and in myopia. The latter as an indication was strongly criticized during the discussion which followed. Franceschetti and Maeder (Geneva) described a new form of corneal dystrophy which they observed in a patient with ichthyosis. Pinchon (Rouen) brought two cases of Fuchs's syndrome in which x-rays showed traumatic lesions of the lower cervical vertebrae. Hugonnier (Lyons) read a paper on surgery in diplopia. Surgical correction should be undertaken only after several months, and when the diplopia is stabilized. The choice of the muscle for operation is often difficult, and the Hess-Lancaster method is of great help. Dejean, Thibault, and Paycha (Montpellier) stated that radioactive phosphorus ions attached themselves almost only to abnormal tissue. Results, however, were not very helpful in three cases of suspected intraocular tumor. Valière-Vialeix and Robin (Limoges) remain faithful to the original Lagrange operation in glaucoma. To make it easier, they make an ab externo incision.

Thursday, May 27, was also given to free papers. Legrand (Nantes) has experimented with plastic transplants in cases in which the usual corneal transplant has become opaque. Appelmans, Michiels, and Jansen (Louvain) reported a case of bilateral exophthalmos which was due to metastasis occurring one year after a breast operation in a woman aged 36. Plessier (Paris) reported a case of malignant exophthalmos in Graves's disease, leading to blindness and death. Hervouët, Lenoir, and Chavannes (Nantes) read a paper on the pathology of the pterygium. Cochet (Paris) reported a case of Kussmaul-Maier disease with uveitis and sclerokeratitis. Corticotropin proved useful. Joly and Lavat (Paris) examined 30 twins and photographed their fundi; this proved useful to show whether or not the twins were identical. Goldmann (Berne) described a new tonometer; the flattening of the cornea is watched with the slit lamp, and the measurement is very accurate. Jarry, Jarlot, and Lhuillier (Paris) followed up 100 patients operated on for glaucoma several years previously; long-term results were far better when the patient had been operated on early, before loss of visual acuity or large field defects. Jayle, Camo, and Ansaldi (Marseilles) examined 50 patients for night vision and found a moving picture very useful. Fritz (Brussels), by paralyzing the ciliary ganglion with procaine, found that the capillary pressure is lowered in glaucoma.

Spontaneous rises of this capillary blood pressure are suppressed, as well as the increase which normally results from electrical stimulation of the cervical sympathetic nerve.

During this five-day meeting there were operating sessions and clinical demonstrations in many hospitals. One of the most interesting was that of Mme. Delthil, in the Lariboisière Hospital, on aniseikonia and the space-eikonometer, the latter being as yet very little known on the Continent.

On Tuesday evening, May 25, the banquet was held at the Pavillon Dauphine, on the outskirts of the Bois de Boulogne, a very pleasant gathering, with Arruga, of Barcelona, presiding. The next afternoon an excursion was organized to Chantilly, where the Château and its grounds were opened to the members of the Congress and their families. The guests were shown around by the curator and were given the opportunity to admire maps, miniatures, manuscripts, and paintings of great interest which are not usually made public.

Several other ophthalmological organizations met during the same week—in particular, the League Against Trachoma, the Paris Society of Ophthalmology, and the Entretiens therapeutiques.

The 62d meeting of the Société française d'ophtalmologie will be held in Paris, May 8 to 12, 1955.

EDWARD HARTMANN, M.D.

NOTICE

The Annual Meeting of the American Medical Association will be held in Atlantic City, June 6-10, 1955. Physicians hoping to take part in that meeting should communicate with their Section officers as early as possible. Deadlines have been set, after which applications will be considered only if there are withdrawals in the program.

DEADLINE FOR SECTION PAPERS, Dec. 15, 1954

DEADLINE FOR SCIENTIFIC EXHIBIT, Jan. 10, 1955

Communications should be addressed to the following:

Section on Ophthalmology

Secretary—Harold G. Scheie, M.D., 313 S. 17th St., Philadelphia 3.

Representative to Scientific Exhibit—William F. Hughes Jr., M.D., 1853 W. Polk St., Chicago 12.

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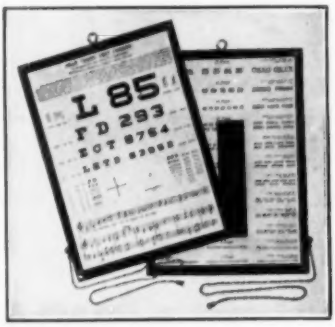

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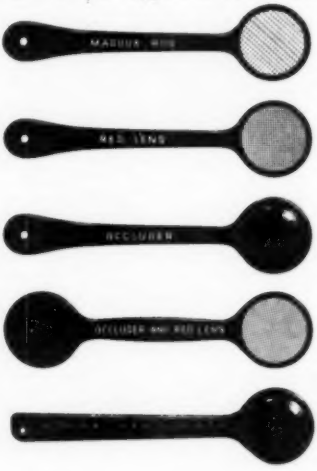

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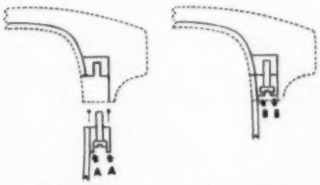

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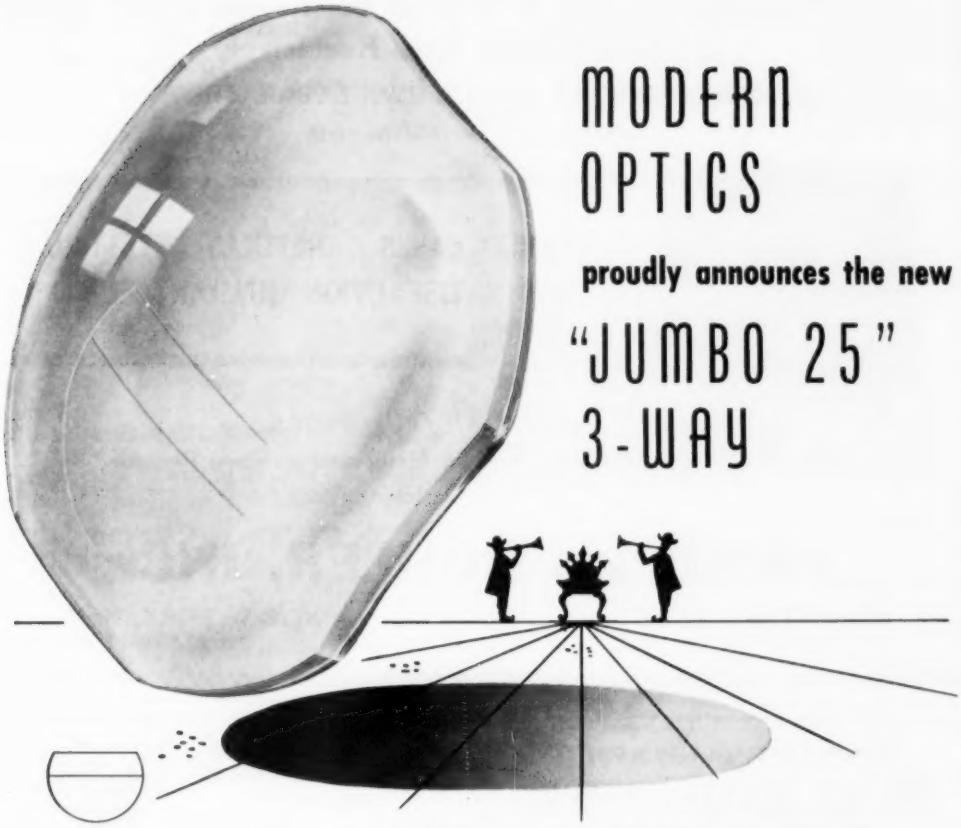

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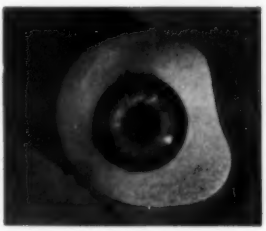

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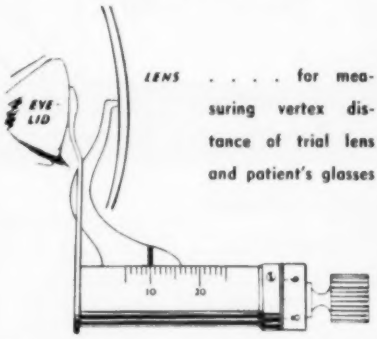

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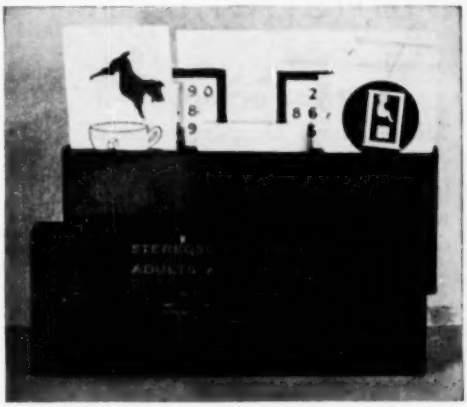

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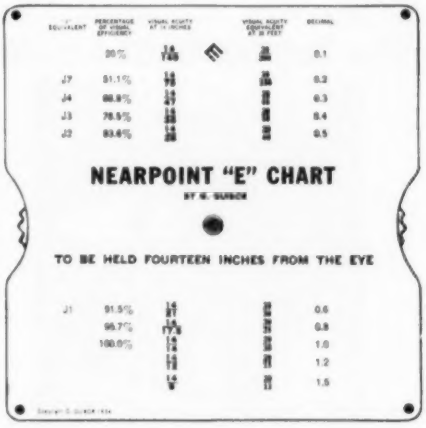

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THAT binocular functions are lost in reverse order of their appearance, i. e., dissolution occurs first at the foveae and spreads progressively to the macular, paramacular and lastly to the peripheral areas;

THAT the First Law of Learning is: The Educational Process should advance *from the known to the unknown;*

does it not follow

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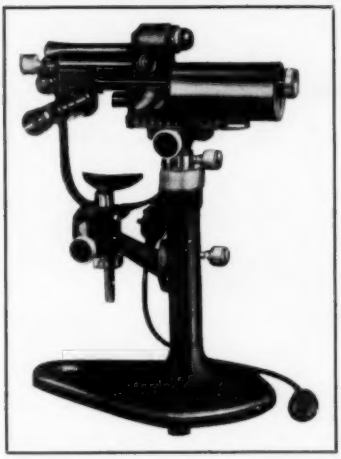

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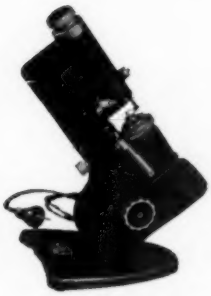

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This statement of the Guild's purpose is reprinted from the cover of the REFERENCE LIST OF GUILD OPTICIANS, a geographical index of all our members. If you would like a copy, just drop a two-penny post card to

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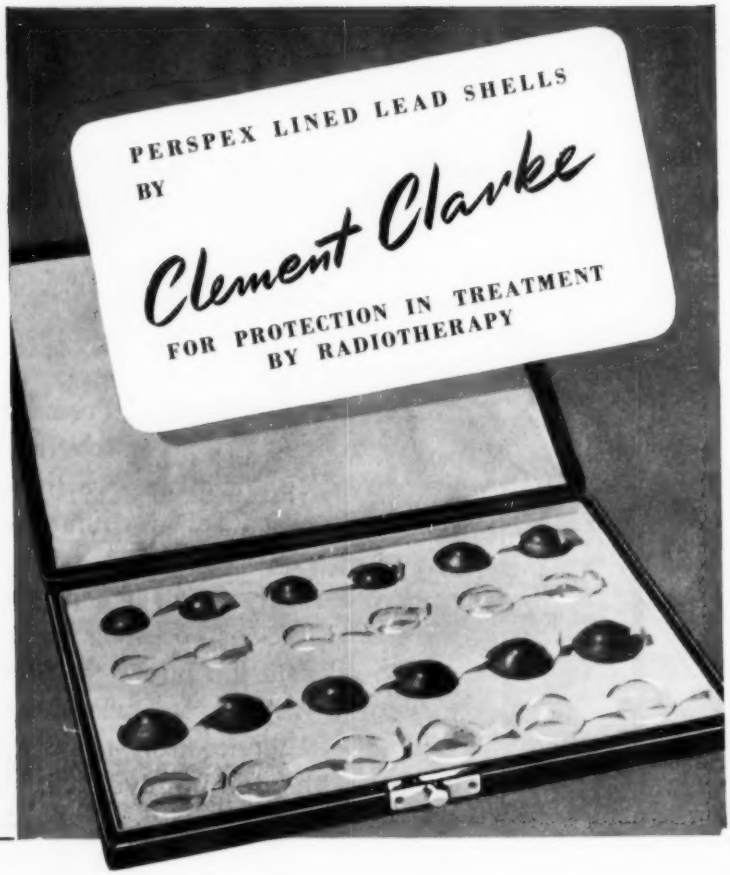

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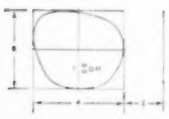

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* Sight Saving Review, Winter 1953 issue

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